INVESTIGATION OF NEW SYNTHETIC REACTIONS: THE SYNTHESIS OF HYDRAZINES VIA THE AZA-LOSSEN REARRANGEMENT, THE SYNTHESIS OF CARBAMOYL AZIDES FROM AMINES, AND DEPROTECTION REACTIONS USING WATER AT ELEVATED TEMPERATURES

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Presented to
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by

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The person you become today is rooted in the person you used to be. As I look back at the person I used to be, I am amazed at how far I have come. But I can take no credit for heights I have reached. To quote Isaac Newton: “If I have seen further it is by standing on the shoulders of giants”. I am truly fortunate to have so many giants in my life. For the past 4 years, I was able to work and grow with two true giants in science. My advisor, Dr. Charles Liotta, taught me that science is more than data. As a long time pessimist, he showed me that everything has a bright side if you just shed a positive light on it. My co-advisor, Dr. Charles Eckert, enlightened me to the world of effective communication. An idea is only as good as others understand it to be. If I have done anything great in my graduate career it is only a reflection of these two mentors.

I would also like to thank the giants of my youth. I was given a solid foundation from my family. I was truly raised by a “village” of amazing giants. My mother and father, Angie Alamo and Miguel Mojica, provided me with more than anything I could have asked for. I believe my ability to work hard and be persistent came directly from their example. You two started from the bottom and now you are here. My grandfather and grandmother, Andres and Maria Mojica, taught me the true meaning of sacrifice. My step-mother, Sherita Mojica, and my brother, Danny Rodriguez, opened the doors to their homes and hearts when they did not have to and for that I am forever grateful.

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LIST OF SYMBOLS AND ABBREVIATIONS

Et	Ethyl
Me	Methyl
Ac	Acetate
Ph	Phenyl
Py	Pyridine
S_N2	Nucleophilic Substitution (bi-molecular)
DMF	Dimethylformamide
Ar	Aryl
Ts	Tosyl
DCM	Dichloromethane
M.P.	Melting Point
MSH	*O*-Mesitylenesulfonatehydroxylamine
TEA	Triethylamine
Mst	Mesityl
NMR	Nuclear Magnetic Resonance
Eqv.	Equivalent
Nr	Number
HOS	Hydroxylamine-*O*-sulfonic acid
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Boc	*Tert*-butoxy carbonyl
t-Bu	*Tert*-butyl
FTIR	Fourier Transform Infared

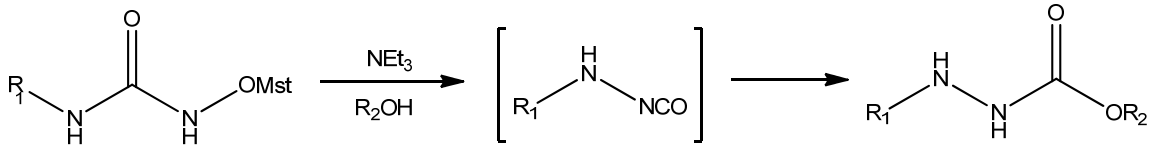
MS	Mass Spectrometry
HRMS	High Resolution Mass Spectrometry
EI	Electron Ionization
ESI	Electrospray Ionization
EA	Elemental Analysis
Δ	Heat
ACN	Acetonitrile
NCS	*N*-chlorosuccinimide
PhTMG	Phenyltetramethyl Guanidine
DPPA	Diphenyl Phosphoryl Azide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
EI	Electron Ionization
RT	Room Temperature
WET	Water at Elevated Temperatures
ε	Dielectric Constant
Piv	Pivaloyl Group
HPLC	High Pressure Liquid Chromatography
p	Para
LC-MS	Liquid Chromatography- Mass Spectroscopy
UV	Ultra Violet
DSC	Differential Scanning Calorimetry
TGA	Thremogravimetric Analysis
CDI	Carbonyldiimidazole
DMSO	Dimethyl Sulfoxide
MTBE	Methyl *Tert*-butyl Ether

SUMMARY

CHAPTER 1: SYNTHESIS OF SUBSTITUTED HYDRAZINES: INTRAMOLECULAR FORMATION OF N-N BONDS VIA THE AZA-LOSSEN REARRANGEMENT

Ester protected monosubstituted hydrazine compounds are found in many important biologically relevant chemicals. Diazane (H_2N-NH_2) is often used as a starting material in the beginning of the synthesis of a complex molecule, but is highly toxic and reactive towards many functional groups. One example of substituted hydrazine formation using mild conditions is a Lossen type reaction (Aza-Lossen), but examples of these reactions exhibit poor overall yield (39%) and has not been investigated thoroughly (only carried out with R=Phenyl). This chapter demonstrates that the reaction is optimal under "infinite dilution" conditions improving yields improved from 39% to 84%. For the first time, other examples of the Aza-Lossen reaction where R= substituted aryl and alkyl groups were successful in synthesizing a methyl ester protected, monosubstituted hydrazine.

Aza-Lossen Reaction

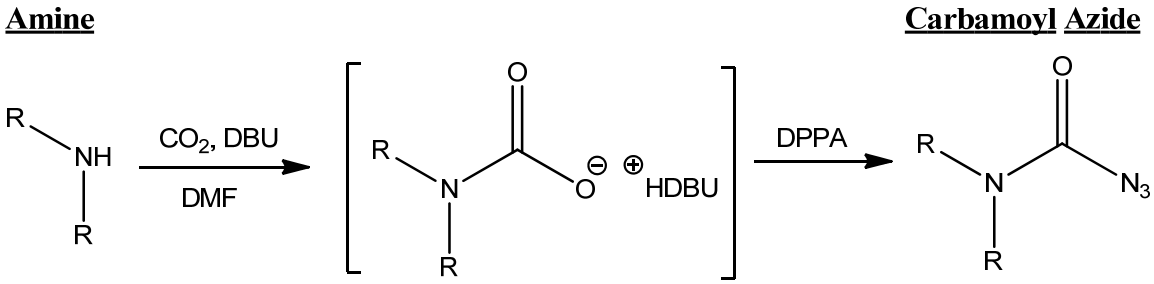


R_1 = Aryl, Alkyl
R_2 = Me, t-But

Since the Aza-Lossen reaction requires an *O*-protected leaving group, several *O*-leaving groups were studied for efficiency. It was discovered that the *O*-mesityl leaving group (OMst) was the best candidate for the reaction. Lastly, the deprotection of the methyl ester from the hydrazine moiety was explored. This class of hydrazines is very stable to acidic conditions and very sensitive to side reactions with very basic conditions. However, an example of a *tert*-butyl ester protected hydrazine was successfully synthesized (35% yield), which can easily be deprotected to the free mono-substituted hydrazine with HCl in methanol.

CHAPTER 2: SYNTHESIS OF CARBAMOYL AZIDES FROM AMINES USING CO_2 AT AMBIENT CONDITIONS

Carbamoyl azides (N_3-(C=O)-NR'R") are a rare class of compounds, but have importance in the synthesis of biologically active compounds and industrial additives. The synthesis of carbamoyl azides usually involves corrosive or explosive starting materials. Recently, carbamoyl azides have been synthesized from more benign reagents, but were limited to only alkyl examples of mono- and disubstituted carbamoyl azides. Also, the reaction conditions (-40°C for mono- and 60°C for disubstituted) were not optimal for large scale synthesis and the base used in the reaction (PhTMG) is not commercially available. This chapter demonstrated that alkyl and aryl mono- and disubstituted carbamoyl azides can be synthesized at ambient conditions.

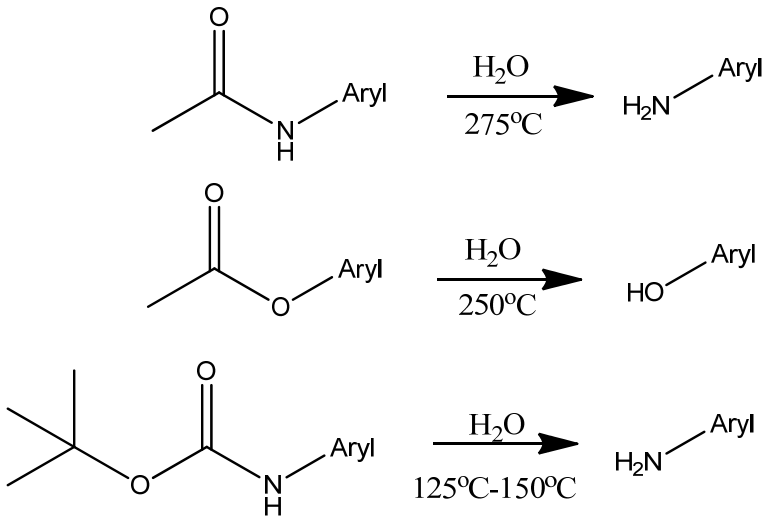


DBU, a commercially available base, performed very well in the reactions and can replace PhTMG. It was also discovered that CsN_3 improves the yield of all reactions and can synthesis carbamoyl azides that could be formed with NaN_3. This improvement in the synthesis is attributed to the "cesium effect", a phenomena in reaction improvement seen throughout literature.

CHAPTER 3: WATER AT ELEVATED TEMPERATURES (WET): A REACTANT, CATALYST, AND SOLVENT IN THE SELECTIVE REMOVAL OF PROTECTING GROUPS

The protection and deprotection of key functional groups is imperative to multistep synthesis of organic molecules. The most popular method of deprotection of protecting groups is with acidic or basic conditions. This method of deprotection is effective, but requires a neutralization step that can produce a large amount of salt waste. Deprotection of protecting groups in water (T > 100°C) could be a possible method to avoid using excess acids and bases. The properties (dielectric constant, $pK_{w)}$ of liquid water over 100°C (under pressure) are suitable for dissolving organic compounds and deprotection reactions with dissociated H^+ and OH^- ions. In this chapter, it is demonstrated that the deprotection of NBoc (carbamate), NAc (amide), and OAc (acetyl) is selective in high yield at 125°C-150°C, 250°C, 275°C, respectively in water. Acetyl group (OAc)

deprotection performed poorly in oxygen rich atmosphere, but was completed in high yield in an N_2 atmosphere and de-oxygenated water.



CHAPTER 1: SYNTHESIS OF SUBSTITUTED HYDRAZINES: INTRAMOLECULAR FORMATION OF N-N BONDS VIA THE AZA-LOSSEN REARRANGEMENT

1.1 Substituted Hydrazine Overview

1.1.1 Substituted Hydrazine Importance

Ester protected, monosubstituted hydrazines, such as alkyl 2-hydrazine aryl carboxylates [1-6] and alkyl 2-hydrazine aliphatic carboxylates [7-9], have been found to be important intermediates in many studies using hydrazine containing molecules. Also, the deprotected, free mono-substituted hydrazines are found in a wide variety of biologically active compounds [10-13] and intermediates (Fisher Indolization). [14, 15] Figure 1.1 outlines several important ester protected and unprotected monosubstituted hydrazine intermediates and compounds.

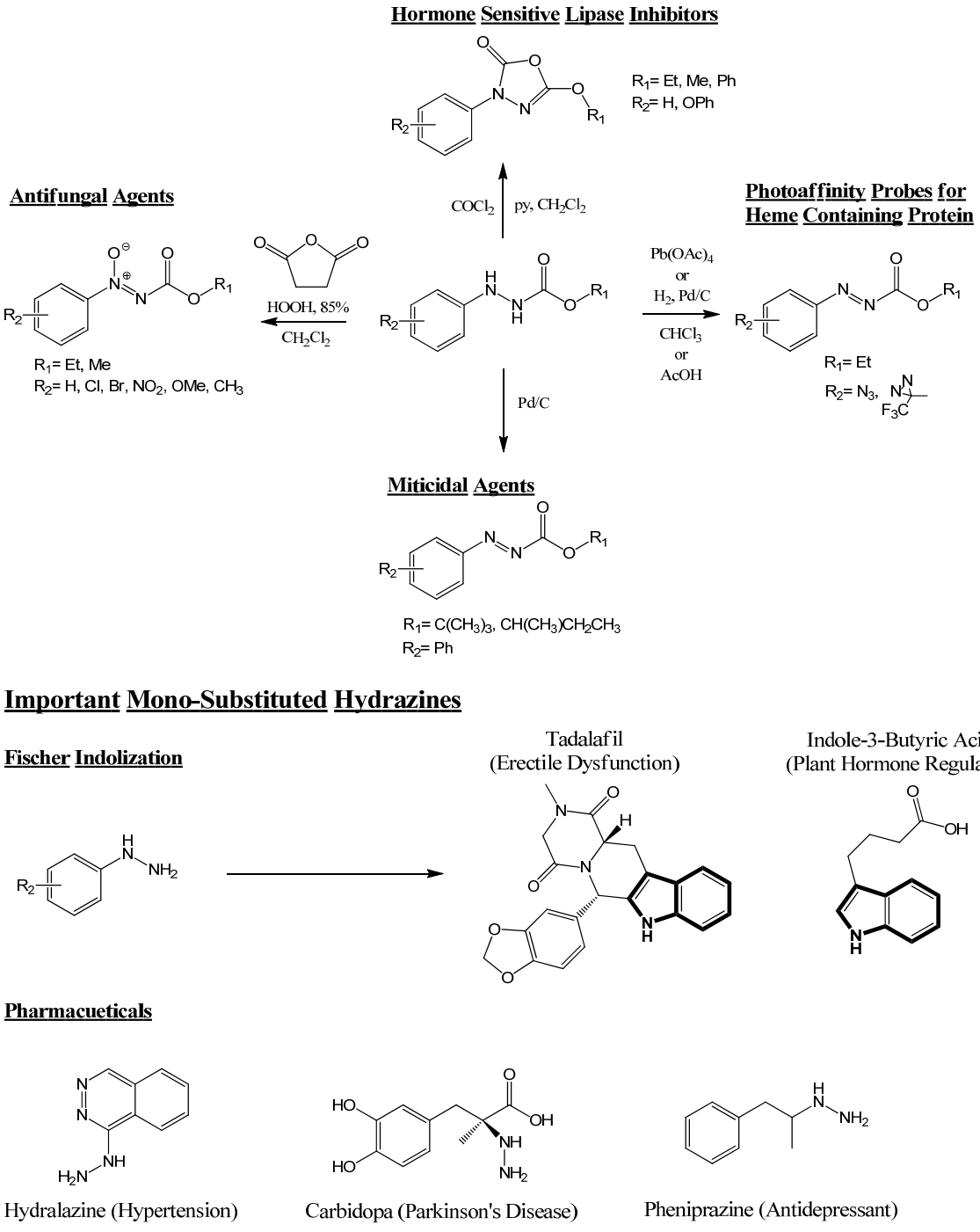


Figure 1.1: Examples of biologically relevant ester protected and un-protected mono-substituted hydrazines

1.1.2 Substituted Hydrazine Synthesis

The hydrazine moieties for these products and intermediates are most commonly produced from either a S_N2 reaction using diazane (H_2N-N_2H) as a nucleophile [16], a reduction of an aryl diazonium salt [17], a reduction of a hydrazone [18-20], or a direct amination of amine compound. [21] Some these examples are outlined in Figure 1.2.

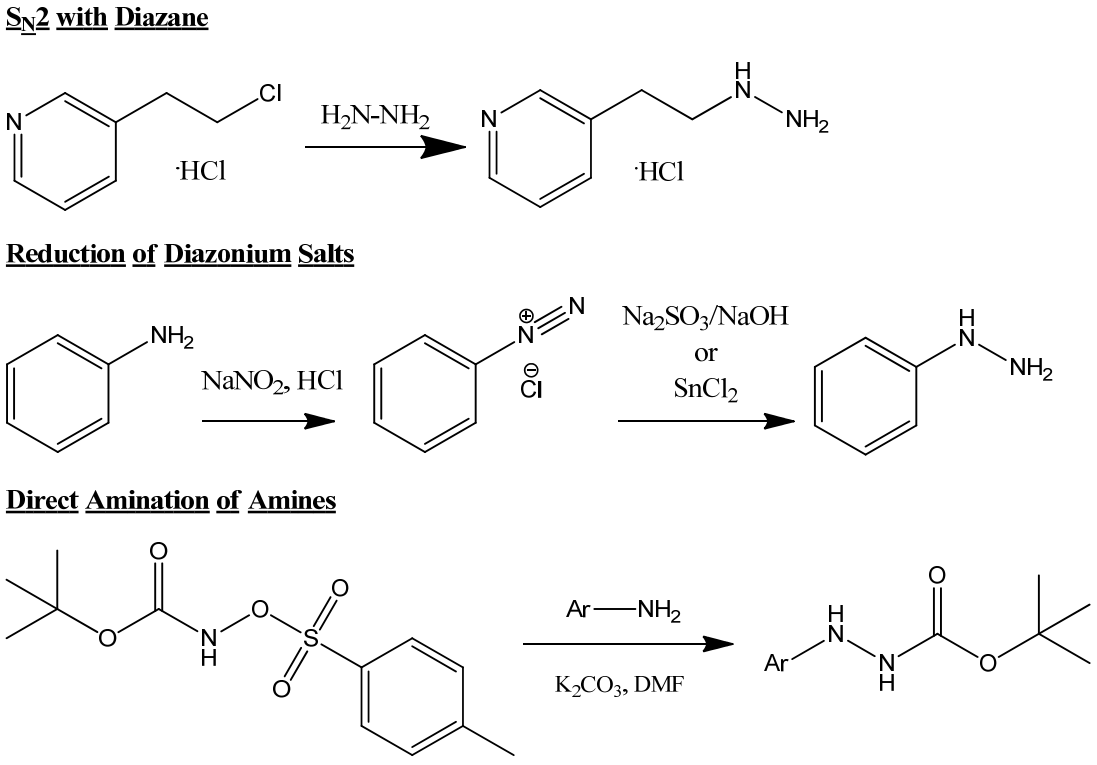


Figure 1.2: Examples syntheses of mono-substituted and ester protected mono-substituted hydrazines

Despite the acceptance of these procedures in literature, there are many limitations that can be improved upon to meet today's standards. For instance, the use of diazane can be problematic due to its volatility, high reactivity and toxicity. [22] Generally, aryl

hydrazine synthesis from a diazonium salt requires a reduction using excess sodium sulfite in sodium hydroxide [23] or toxic and reactive tin (II) chloride. [24] Finally, formation of a N-N bond by direct aminations of monosubstituted amines to which is attached a good leaving group by another amine suffer from a number of weaknesses including the instability of the electrophilic amine. [25, 26]. Not only do the above examples employ rather harsh conditions, there are additional issues with regard to safety, work-up, and waste problems. In addition, the presence of reactive functional groups can interfere with the efficiency of the reaction. Thus, the most common synthetic approaches involves building a molecule around an already formed N-N bond, rather than form an N-N bond during later steps in a multistep synthetic sequence.

1.2 The Lossen Reaction

1.2.1 The Classical Lossen Reaction and Aza-Lossen Reaction Analogue

The preparation of hydrazines using milder conditions could present the pharmaceutical industry with new strategies to prepare increasingly complex biologically molecules. Recent articles continue to explore new strategies. [27-30] However, there exist in literature singular examples of hydrazine synthesis using rearrangement reactions that seem to be most promising toward the development of general and mild preparative methods. [31-34] One of these singular examples is a paper published in 1974 in which

the authors demonstrated *one example* of an aza-counterpart of the Lossen rearrangement to produce phenylhydrazine (Figure 1.3). [35]

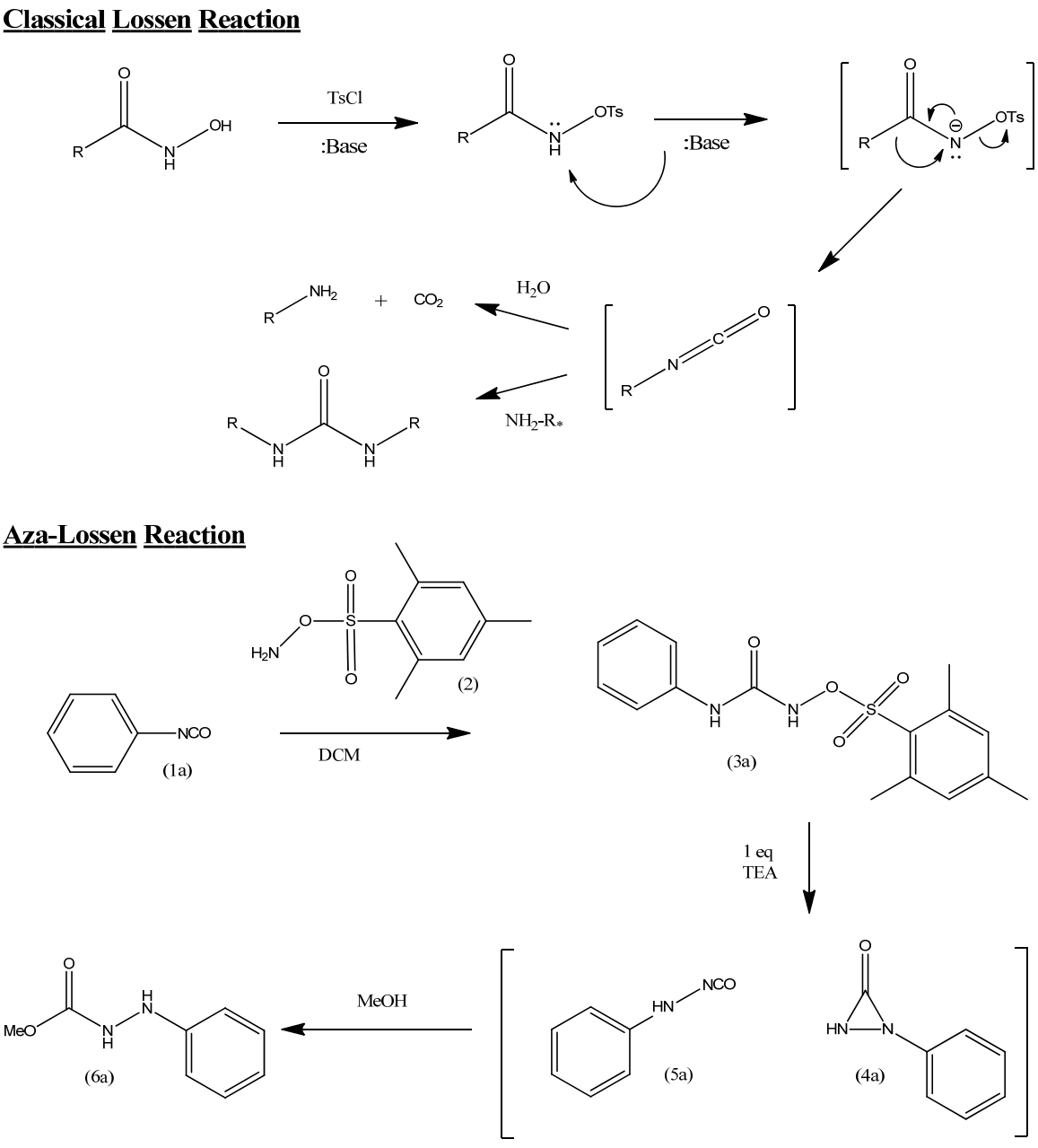


Figure 1.3: Synthesis and possible intermediates for the formation of methyl-2-phenylhydrazine carboxylate via an Aza-Lossen Rearrangement [35]

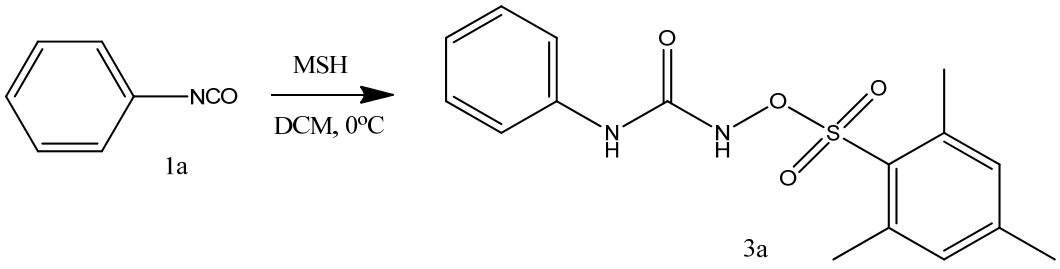
The aza- counterpart will be subsequently referred to as the Aza-Lossen rearrangement. In this particular case, the starting material was an un-symmetrically substituted urea (3a) in which the migrating group is an aminophenyl substituent and the leaving group is mesitylene sulphonate. A base promoted alpha elimination in methanol lead to N-N bond formation (methyl 2-phenylhydrazinecarboxylate (6a)) in a rearrangement process. It was postulated that the reaction proceeds through two possible intermediates: an aminoisocyanate (5a) or a diaziridinone (4a). The study only theorizes these intermediates and do not offer any experimental explanations to which is most reasonable. Subsequent publications have observed aminoisocyanates (5) as an intermediate of a similar photolysis rearrangement reaction. Other aminoisocyanate type compounds (RR'-NNCO) have only been observed in inert gas matrices. [36] In contrast, the diaziridinone (4a) has been isolated and found in literature to be a stable species (M.P.=190°C). [37]

1.2.2 Optimization of the 1-((mesitylsulfonyl)oxy)-3-phenylurea Reaction

This single reaction example opened the door for possible new methodologies for the formation of hydrazine compounds via an intramolecular reaction. Yet there has been no further investigation of this reaction to establish its full synthetic scope. The original reaction reported a relatively low isolated yield of both the urea starting material (3a) at 61% and the hydrazine derivative (6a) at 39%. In addition, the Aza-Lossen reaction was performed in an extremely dilute system (1 mmol substrate/100 mL methanol), which, by

all intents and purposes, is not practical for scale-up. Therefore, it became important to understand the important variables in order to optimize the yields in both steps of the reaction sequence the urea formation and the Aza-Lossen rearrangement. Herein is presented the results of our investigation in the syntheses of ester 2-carboxylate protected, monosubstituted hydrazines. The reactions of the original literature procedures were repeated in our laboratory. Our experimental yield of the urea starting material (3a, 64%) and the crude yield of hydrazine product (6a, 30%) agreed amazingly well with the original procedure and reported yield. Nevertheless, the yield of the intermediate urea derivative and the final hydrazine product was far too low to be of synthetic use. It is well-known that *O*-mesitylenesulfonatehydroxylamine (MSH) (2), an *O*-protected hydroxylamine, decomposes rapidly upon isolation [26] and could possibly be the source of the modest urea yield (3a). Thus, we studied the effect of increasing the molar equivalents of MSH in its reaction with phenyl isocyanate in the synthesis of the corresponding urea sulfonate.

Table 1.1: Reaction of phenylisocyanate with varying molar equivalents of MSH



1a 3a

Trial	MSH Molar Equivalent	6 (%)
a[1]	1	64
b	1.2	74

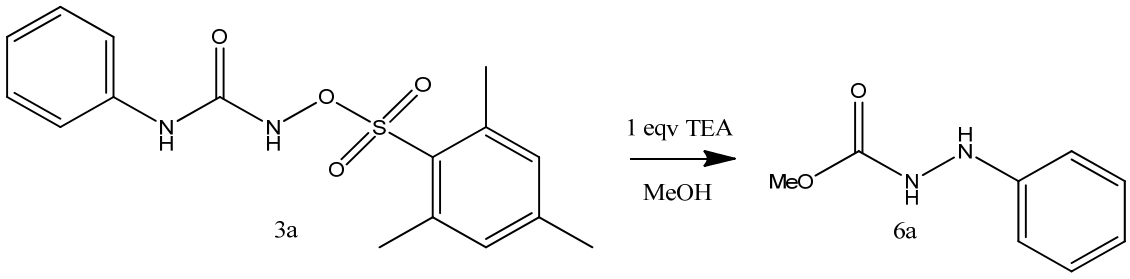
c	1.6	98

It was found that in using 1, 1.2, and 1.6 molar equivalents of (2), the yields of (3a) were 64%, 74%, and 98%, respectively. Thus, the initial postulate that MSH decomposition competes with the desired reaction was supported and adding an excess of this reagent effectively increases the yield of the urea product.

1.2.3 Optimization of the Aza-Lossen Reaction

It has already been pointed out that the literature procedure for conducting the Aza-Lossen rearrangement is employing very dilute conditions. In an attempt to improve the both the yield and the output of hydrazine product, the effect of concentration and temperature on reaction yield was studied.

Table 1.2: Study of temperature and concentration effects of the Aza-Lossen rearrangement reaction



3a 6a

Trial	Temperature (°C)	Concentration (mmol urea : mL MeOH)	Yield (%)
1	0	1:100	30

2	0	1:50	10
3	0	1:10	0
4	-75	1:100	0
5[b]	0	1:100	84[a]
6[b]	20	1:100	61[a]

[a] Isolated yield

[b] Infinite dilution method

First, we investigated concentration effects by experimentally decreasing the amount of methanol solvent to 50 mL and 10 mL (Table 1, Trial 2 and3) while holding all other parameters constant. As the reaction was conducted at higher concentrations, the yield of the desired hydrazine product decreased (as evidenced by ^{13}C NMR). These results indicate that product formation is optimum in highly dilute conditions. We postulate that the aminoisocyanate is a highly reactive species that can react with itself to other non-hydrazine products. As a consequence, we set up the reaction in a way that we could simulate "infinite dilution" in methanol, so the subsequent aminoisocyanate will be preferably reactive toward methanol to trap the hydrazine structure. To achieve "infinite dilution", the base was dissolved in half of the solvent and the urea dissolved in the other half of solvent in a separate vessel. The dissolved urea was then added dropwise to the base at slow rate (Figure 1.4).

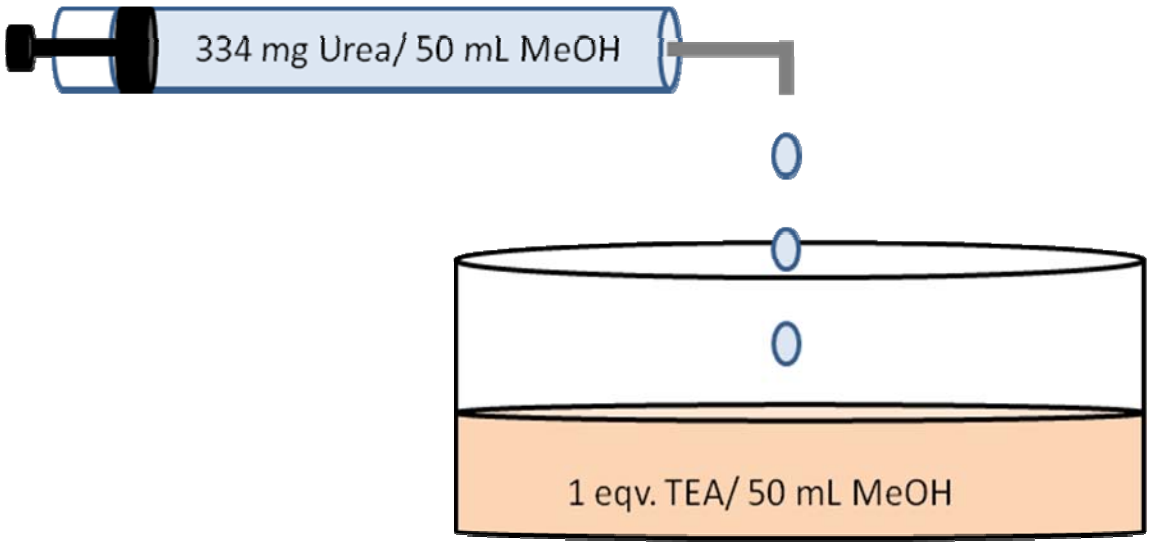


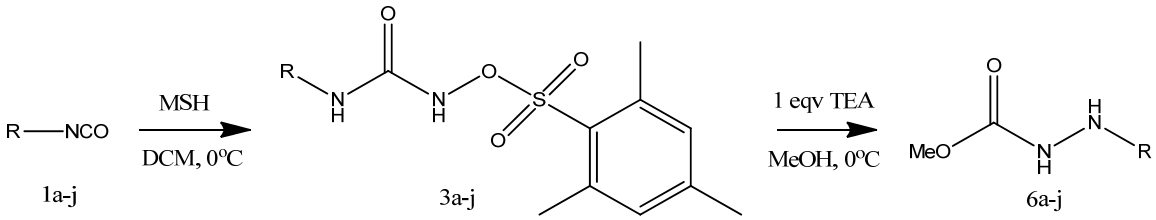
Figure 1.4: Schematic of the Aza-Lossen reaction with the "infinte dilution" method

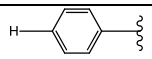
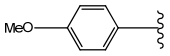
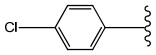
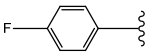
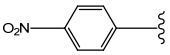
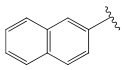
Since the reaction is fast, each drop of urea solution will be consumed by reaction and the concentration of urea inside the reaction vessel will remain close to 0 throughout the reaction. This new methodology was found to improve the yield from 34% to 84% after isolation (Table 1.2, Trial 6). Additional reactions were performed at -75°C and 20°C to investigate the effect of temperature. The base addition procedure at -75°C did not yield any product. The infinite dilution reaction was performed at 20°C yielding to 61% of the product after isolation. These findings suggest that conditions closer to 0°C are preferred.

1.2.4 Aza-Lossen Study with Different Migrating Groups

Using the optimized conditions of the reaction steps in Scheme 1, we investigated the breadth of several different migrating groups for the rearrangement using varying isocyanate starting materials (Table 1.3).

Table 1.3: Aza-Lossen rearrangement with varying migrating groups [38]



Nr	R	3 (%)	6 (%)
a[1]		98	84
b		62	31
c		58	55
d		61	59
e		81	56
f		94	55
g		96	87
h		43	65

[1] Hydrazine synthesized under "infinite dilution" addition method.

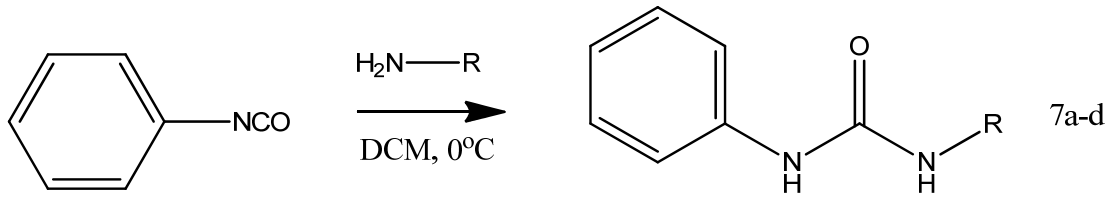
The migrating groups were chosen to study the electron effects on the Aza-Lossen reaction. For example aryl groups (electron withdrawing), alkyl groups (electron

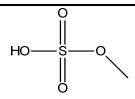
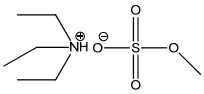
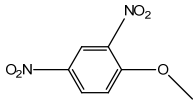
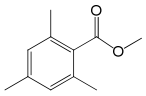
donating), para-halogens (electron withdrawing), para-nitro groups (electron withdrawing), and para-methoxy groups (electron donating) can either decrease or increase electron density around the migrating nitrogen. During the course of the experiment, a modification had to be made. The substituted Aza-Lossen ureas tend to have a reduced solubility in methanol than the original aryl starting material used for optimization. Therefore, all of the compounds were added as a solid portion-wise to the base/solvent mixture. Even though Table 1.3 shows that the Aza-Lossen urea synthesis and Aza-Lossen rearrangement are possible for several aryl and alkyl migrating groups, the data does not suggest a correlation between the yield and electronic effects of the migrating group. However, one observation was made during the experiments that could explain a substituent affect on the yield. As stated before the solubility of the urea compounds in methanol varied based on the migrating group substituents. Of all the synthesized hydrazine compounds from Table 2, the *p*-methoxy aryl urea (3b) had the lowest solubility in methanol (< 1 mg per 1 mL MeOH) and also had the lowest yield (31%) of the rearrangement reaction. The aryl urea (3a) with the highest solubility (5mg dissolves fully in 1 ml MeOH) achieved the highest yield (84%). The solubility effect agrees with our previous hypothesis. The less soluble the starting material in the trapping solution, the more the system will deviate from the "infinite dilution" conditions and generate lower yields of hydrazine.

1.2.5 Aza-Lossen Study with Different Migrating Groups

To further explore the scope of the Aza-Lossen reaction, we looked at using a different *O*-sulfonate hydroxylamine to use as the leaving group (Table 1.3).

Table 1.4: Aza-Lossen rearrangement reaction with varying leaving groups.



Nr	R	Urea Isolated Yield (%)
a		40
b		63
c		62
d		0

Since MSH is not commercially available and not suitable for storage, we explored the use of hydroxylamine-*O*-sulfonic acid (HOS). The reaction of HOS and phenyl isocyanate produced the hydroxylamine sulfonic acid urea (7a) in 40% yield, but decomposed shortly after isolated (white solid evolves purple color after several minutes). To aid in stabilizing the compound, the acid was first reacted with TEA to form a salt and then mixed with phenyl isocyanate to form the urea sulfonic acid salt (7b) in 63% yield. Another urea, 1-(2,4-dinitrophenoxy)-3-phenylurea (7c), was synthesized in

62%, but 1-phenyl-3-((2,4,6-trimethylbenzoyl)oxy)urea (7d) was unsuccessful. This outcome is probably due to the known rearrangement of *O*-(2,4,6-trimethylbenzoyl)hydroxylamine to *N*-hydroxy-2,4,6-trimethylbenzamide (Fig. 1.5). [39]

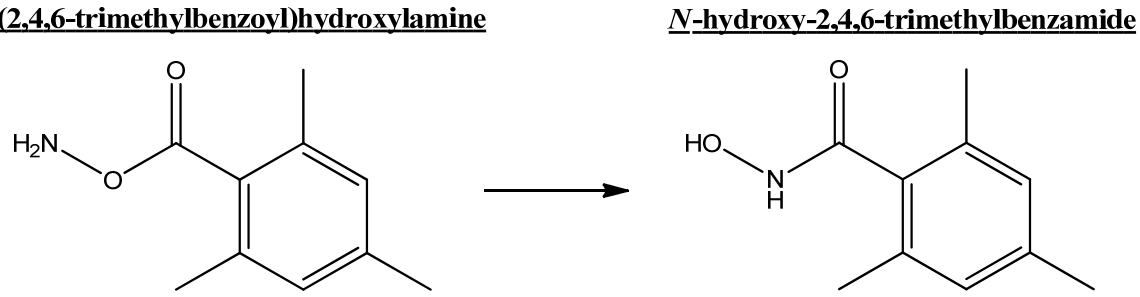


Figure 1.5: The rearrangement of *O*-(2,4,6-trimethylbenzoyl)hydroxylamine to *N*-hydroxy-2,4,6-trimethylbenzamide

Despite the success in synthesizing the new ureas, they were shown to be substandard in forming a hydrazine product via the Aza-Lossen reaction. When the "infinite dilution" Aza-Lossen reaction was attempted with (8b) at 0°C and 20°C, only the starting materials were recovered. When the reaction took place at methanol reflux (62°C), a crude yield of about 30% of the desired hydrazine (6a) was identified in ^{13}C NMR, but a myriad of unidentified byproducts were also generated (Fig. 1.6).

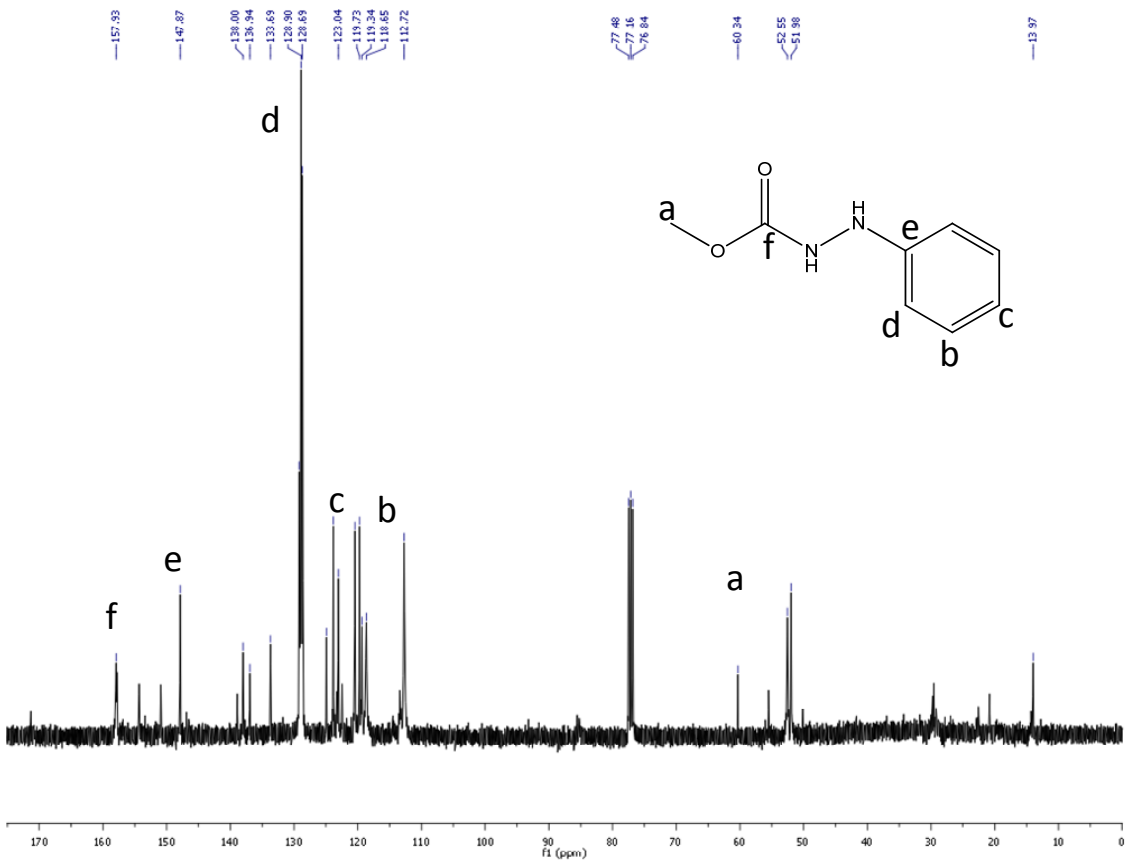


Figure 1.6: ^{13}C NMR of the crude product from the Aza-Lossen reaction of 8b to 6a

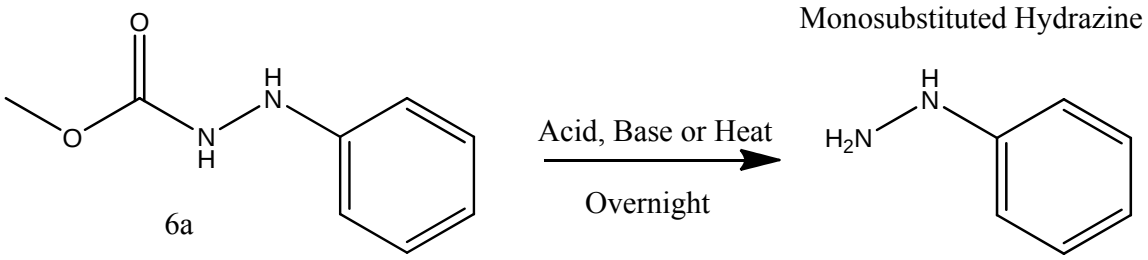
When 7c was reacted in Aza-Lossen conditions, the product analysis showed no evidence of the synthesis of a hydrazine and also yielded many other by-products.

1.2.6 Synthesis of *tert*-butyl 2-phenylhydrazinecarboxylate

It was previously mentioned that the unprotected, free hydrazine is useful in many pharmaceutical applications. Deprotection of methyl esters from hydrazines is rare, but there are examples of the deprotection of disubstituted hydrazines in literature. [40, 41] Unfortunately, there are no reports of the deprotection of methyl 2-hydrazine

carboxylates to mono-substituted hydrazines in literature. We attempted to deprotect methyl 2-phenylhydrazinecarboxylate (6a) to phenyl hydrazine using very acidic conditions (65 eqv. trifluoroacetic acid (TFA) in MeOH), basic conditions (30 eq. potassium hydroxide in dioxane/H_2O) and in H_2O at elevated temperature (150°C closed reactor) (Table 1.5).

Table 1.5: Deprotection of methyl-2-phenylhydrazine using acid, base, and elevated temperatures



6a

Trial	Conditions	Temperature (°C)
1	0.25 g of 6a was added 27 mL of 1.25M HCl-EtOH (20 eqv. HCl)	RT
2	100 mg of 6a in 1 mL MeOH was added to 3 mL of TFA (65 eqv. TFA)	RT
3	100 mg of 6a in 1 mL MeOH was added to 3 mL of TFA (65 eqv. TFA)	40
4	100 mg of 6a in 1 mL MeOH was added to 3 mL of TFA (65 eqv. TFA)	62
5	100 mg of 6a in 9 mL dioxane was added to a solution of 1 g KOH in 9 mL water (30 eqv of KOH)	RT
6	100 mg of 6a in 3 mL THF was added to 3 mL of 1M solution of tetra-*n*-butylammonium fluoride (5 equiv.)	RT
7	4 mg of 6a in 1.5 mL of deoxygenated water in a sealed, stainless-steel reactor under nitrogen	150

All methods were unsuccessful. Compound 6a is very stable to acidic conditions (starting material was fully recovered) and unstable to both bases and high temperatures. Therefore, we explored the synthesis of tert-butoxy carbonyl (Boc) protected hydrazines using the Aza-Lossen reaction. It has been shown in literature that *tert*-butyl ester protected, monosubstituted hydrazines can proceed to a free hydrazine using HCl. [42-44] The Aza-Lossen urea (3a) has poor solubility in *t*-butyl alcohol, so the urea was added portion-wise as a solid. Since *t*-butyl alcohol is a solid at room temperature, the reaction temperature was increased to 30°C. The product (9) was isolated in 35% yield, however the reaction was not optimized under these new conditions. Thus, the Aza-Lossen reaction can be used as a pathway to a monosubstituted hydrazine.

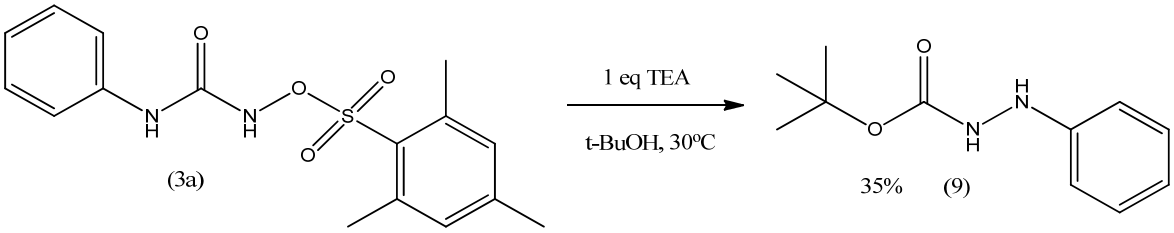


Figure 1.7: Synthesis of tert-butyl 2-phenylhydrazinecarboxylate (9) via an Aza-Lossen Rearrangement.

1.3 Conclusions

In conclusion, we have demonstrated that the Aza-Lossen reaction can be used to produce both 2-aryl and 2-aliphatic carboxylate hydrazines. We indentified that the yields of 1-

((mesitylsulfonyl)oxy)-3-aryl and alkyl ureas can be increased by using 1.6 equivalents of MSH. The Aza-Lossen reaction can be improved using "infinite dilute" conditions due to the sensitivity of the aminoisocyanate intermediate in concentrated solutions. The same procedures can be used to produce *tert*-butyl 2-phenylhydrazinecarboxylate (Boc protected), which can subsequently yield mono-substituted hydrazines. The MSH leaving group was the most effective leaving group tested, as HOS was the only other leaving group that showed evidence of producing a hydrazine but in very low yield.

1.4 Recommendations

The Aza-Lossen reaction is novel method to producing hydrazines without the use of excess diazane or excess acids and bases. However, many aspects of the reaction would need to be improved before such a reaction could be used successfully in industrial settings. While MSH was effective as a leaving group, it is tedious to synthesize and must be used promptly after isolation. Tamura et. al. cited a library of several aminating agents to produce hydrazines compounds[21]. Some of the agents are more stable for storage than MSH and could be just as effective in the Aza-Lossen reaction. Another issue is the large amount of solvent that was used to achieve the most dilute conditions possible. Since the reaction is fast, it may be possible to use less solvent in continuous flow reactor. It also may be suitable to recycle the solvent after evaporation to use in subsequent reaction.

1.5 Experimental

1.5.1 Synthesis Procedures

All solvents and reagents were purchased from commercial sources in reagent grade form and were used without further purification. Nuclear magnetic resonance (NMR) spectra were measured on a 400 MHz Varian (1-D measurements). Mass spectrometry measurements were performed by electron impact (EI) or (ESI) on a Micromass (Waters) Autospec M. Infrared spectroscopy measurements were performed with neat samples on a Shimadzu FTIR Prestige-21 equipped with a Specac Golden Gate ATR cell. Elemental analyses were performed by Atlantic MicroLab, Inc.

Total Synthesis of O-mesitylenesulfonatehydroxylamine (MSH)

Synthesis of tert-butyl hydroxycarbamate: In a 250 mL round bottom flask with a stir bar, 6 g (0.0875 mol) hydroxylamine hydrochloride was added. The solid was mixed with 38 mL diethyl ether and stirred vigorously. To the heterogenous mixture, 6 g (0.0575 mol) of sodium carbonate was added as a solid. 5 mL water was added dropwise. The suspension was stirred for 1 hr, and then cooled to 0°C in an ice bath. A solution of 12.55 g (0.0575 mol) di-*tert*-butyl dicarbonate in 12.5 mL diethyl ether dropwise was added over 30 min at 0°C. The suspension was heated to room temperature and stirred for 3 hr. The reaction mixture was filtered and washed with 2x25 mL diethyl ether. The filtrate was put under vacuum to evaporate the solvent to obtain a colorless mother liquor. Upon addition of cyclohexane, 8.31 g (.6243 mol, 95%) of *tert*-butyl hydroxycarbamate crystallized as colorless needles (2 crops).

Synthesis of tert-butyl (mesitylsulfonyl)oxycarbamate: 3.25 g (0.0147 mol) of 2-mesitylenesulfonyl chloride and 2 g (0.0147 mol) of tert-butyl hydroxycarbamate were added to a three neck 100 mL round bottom flask with a magnetic stirrer. The solids were dissolved in 34 mL of methyl tert ether (MTBE). The flask was purged with Argon gas and cooled to 0°C in an ice bath. To the solution, 2.1 mL (0.015 mol) of Triethylamine was added dropwise over 1.5 hr (ammonium hydrochloride precipitated). The reaction was allowed to reach room temperature and stirred for an additional 2 hr. After completion, the ammonium hydrochloride salt was filtered and washed with MTBE. The organic solvent was evaporated using rotary evaporation until mother liquor was obtained. Tert-butyl (mesitylsulfonyl)oxycarbamate (4.26 g, 0.0135 mol, 92%) was precipitated as clear needles when hexane was added.

Synthesis of O-mesitylenesulfonatehydroxylamine: 2.3 g (0.0073 mol) of *N*-Boc-*O*-mesitylenesulfonylhydroxylamine was added to a 25 mL round bottom flask equipped with a stir bar. The flask was purged with with argon and cooled to 0°C in an ice-water bath. 7 mL of cold TFA was added and mixed for 1 hr at 0°C. The reaction mixture was poured onto ice water to precipitate a white solid. The crude solid was filtered and washed with water. Cold DCM was added to dissolve the solid and the organic solvent was added to a separatory funnel with cold water. The organic layer was dried with $MgSO_4$, filtered, and the solvent under vacuum. 1.52 g (.0071 mol, 97%) white solid was isolated.

Representative Experimental Synthesis of the Mesitylsulfonyl-ureas

1.6 molar equivalents of O-(mesitylsulfonyl)hydroxylamine was dissolved in 20mL of anhydrous dichloromethane in a 100mL round bottom flask equipped with a stirring bar. The reaction mixture was cooled in an ice water bath and 1 molar equivalent of isocyanate was added drop-wise. After addition, the reaction was allowed to reach room temperature and stirred overnight. The dichloromethane was removed under vacuum and the resulting solid was recrystallized from hot methanol.

Representative Experimental Procedure for the Aza-Lossen Reaction Base Addition

334 mg (1 mmol) of 1-((mesitylsulfonyl)oxy)-3-phenylurea (3a) was added to a 250 mL round bottom flask equipped with a stir bar. 100 mL anhydrous methanol was added under nitrogen and was stirred for 10 minutes. The reaction mixture was cooled to 0°C in an ice water bath. 0.14 mL (1mmol, 101 mg) of triethylamine was added dropwise. The reaction mixture evolves a yellow color. After addition of base was complete, the reaction was allowed to reach room temperature and stirred overnight. After the reaction, the solvent was removed under vacuum to obtain a yellow solid. The solid was purified on an alumina column (pH=7.2) using 9:1 hexane: ethyl acetate as the eluent.

Representative Experimental Procedure for the Aza-Lossen Reaction Infinite Dilution

334 mg (1 mmol) of 1-((mesitylsulfonyl)oxy)-3-phenylurea (3a) was dissolved in 50 mL of anhydrous methanol and loaded into a 100 mL syringe pump. In a separate 250 mL round bottom flask, 0.14 mL (1 mmol, 101 mg) of triethylamine (TEA) was dissolved in 50mL anhydrous methanol under nitrogen and was stirred for 10 minutes. The

TEA/methanol mixture was cooled to 0°C in an ice water bath. The urea/methanol solution was added over 3 hours to the TEA/methanol mixture. The reaction mixture evolves a yellow color. After the addition of the urea was complete, the reaction was allowed to reach room temperature and stirred overnight. After the reaction, the solvent was removed under vacuum to obtain a yellow solid. The solid was purified on an alumina column (pH=7.2) using 9:1 hexane: ethyl acetate as the eluent.

Representative Experimental Procedure for the Aza-Lossen Reaction with Varying Migrating Groups

In a 250 mL round bottom flask, 0.14 mL (1 mmol, 101 mg) of triethylamine (TEA) was dissolved in 100mL anhydrous methanol under nitrogen and was stirred for 10 minutes. The TEA/methanol mixture was cooled to 0°C in an ice water bath. 1mmol of mesitylsulfonylurea solid was added portionwise over 2 hours. After the addition of the urea was complete, the reaction was allowed to reach room temperature and stirred overnight. After the reaction, the solvent was removed under vacuum to obtain a yellow solid. The solid was purified on an alumina column (pH=7.2) using 9:1 hexane: ethyl acetate as the eluent.

Synthesis of ((3-phenylureido)oxy)sulfonic acid

In a 50 mL flask with stir bar, 1 g (0.009 mol) of *O*-hydroxylamine-sulfonic acid was added and purged with nitrogen. 7 mL of dimethylformamide was added and stirred until the solid was dissolved. The flask was cooled in an ice water bath. 1 mL (0.009 mol) of phenylisocyanate was added dropwise to the mixture. The reaction was stirred for 4 hr

and the reaction became yellow and cloudy. The product was isolated by adding dichloromethane to the flask to precipitate a white solid. The white solid product was dried for 1 hour, but developed a purple color. Heating the solid above 60°C caused the compound to decompose.

Synthesis of triethylammonium 3-phenylureido sulfate

In a 50 mL flask equipped with a stir bar, 1 g (0.0090 mol) of O-hydroxylamine-sulfonic acid was added. The reaction vessel was purged with nitrogen and 15 mL of dichloromethane was added while stirring (a suspension was formed). The vessel was cooled in an ice water bath and 0.6 mL (0.0045 mol) of triethylamine was added dropwise to mixture to obtain. 0.5 mL (0.0045 mol) of phenylisocyanate was then added dropwise to mixture and stirred for 4 hrs. The solid was filtered from the reaction mixture and the solvent was removed by rotary evaporation and resulted in a viscous oil.

Experimental Procedure for *tert*-butyl 2-phenylhydrazine carboxylate

In a 250 mL round bottom flask, 0.14 mL (1 mmol, 101 mg) of triethylamine (TEA) was dissolved in 100mL anhydrous *t*-butyl alcohol at 30°C under nitrogen and was stirred for 10 minutes. 334 mg (1 mmol) of 1-((mesitylsulfonyl)oxy)-3-phenylurea (3a) was added portionwise over 2 hours. After the addition of the urea was complete, the reaction was allowed to reach room temperature and stirred overnight. After the reaction, the solvent was removed under vacuum to obtain a yellow solid. The solid was purified on an alumina column (pH=7.2) using 9:1 hexane: ethyl acetate as the eluent.

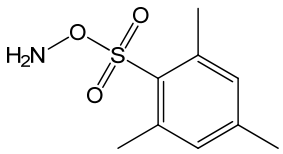
Experimental Procedure for 1-(2,4-dinitrophenoxy)-3-phenylurea

To a 25 mL flask, 2.5 g of *N*-Boc-*O*-dinitrobenzene was added to 7 mL of neat TFA at 0°C. After 1 hr, the solution was poured into ice. The precipitate was filtered and rinsed with excess water. The organics were extracted with DCM, dried with $MgSO_4$, and the solvent evaporated to obtain approximately 1g (0.005 mol) of *O*-(2,4-dinitrophenyl)hydroxylamine. This was immediately dissolved in 20 mL DCM in 100mL flask and cooled in an ice bath. 0.55 mL (0.005 mol) of phenyl urea was added dropwise and stirred overnight. The product was recrystallized from hot methanol, filtered, and dried in a vacuum oven. 1.59 g of crude product recovered (62% crude yield).

Experimental Procedure for methyl 2-phenylhydrazine carboxylate (9) from (8b)

In a 250 mL, three-neck, round bottom flask fitted with a condenser, 0.14 mL (1 mmol, 101 mg) of triethylamine (TEA) was dissolved in 50 mL anhydrous methanol and heated reflux under nitrogen. In a syringe pump 333 mg (1 mmol) of 8b was added to 50 mL of anhydrous methanol. The addition of the urea solution to the TEA/methanol solutions was done with a flow rate of 1.3 mL/hr at reflux. After addition, the reaction was cooled and the solvent was removed under vacuum to obtain a crude, yellow oil.

1.5.2 Spectral Data



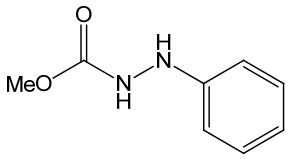
O-mesitylenesulfonatehydroxylamine (MSH)

Color and State: Clear needles

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.63 (s, 6H), 5.72 (s, 2H), 6.99 (s, 2H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 142.20, 136.83, 136.06, 130.11, 22.84, 20.41.

MP: 68-70°C



methyl 2-phenylhydrazinecarboxylate

Color and State: White solid

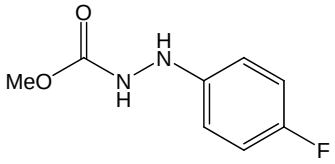
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 5.53 (s, broad 1H), 6.73 (s, broad 1H), 6.81-6.77 (d, 2H), 6.90-6.86 (t, 1H), 7.23-7.19 (t, 2H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 157.78, 147.94, 129.28, 121.06, 113.10, 52.98.

MP: 108-110°C

HRMS ($C_8H_{10}N_2O_2$) Exact Mass Calculated: 166.0738 Found: 166.0742

EA Theoretical: 57.82 (C%), 6.07 (H%), 16.86 (N%); Found: 58.56 (C%), 6.20 (H%), 16.31 (N%)



methyl 2-(4-fluorophenyl)hydrazinecarboxylate

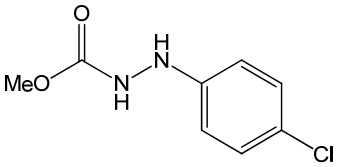
Color and State: Yellow solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 5.74 (s, broad 1H), 6.62 (s, broad 1H), 6.78-6.77 (t, 2H), 6.94-6.91 (t, 2H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 157.69, 144.03, 115.82, 115.60, 114.33, 52.93.

HRMS ($C_{11}H_{16}N_2O_2$) Exact Mass Calculated: 184.0642 Found: 184.0648

MP: 114-116°C



methyl 2-(4-chlorophenyl)hydrazinecarboxylate

Color and State: Beige solid

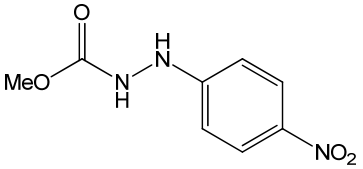
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 5.86 (s, broad 1H), 6.67 (s, broad 1H), 7.19-7.16 (d, 2H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 157.68, 146.67, 129.25, 125.85, 114.37, 53.14.

HRMS ($C_{11}H_{16}N_2O_2$) Exact Mass Calculated: 200.0347 Found: 200.0353

EA Theoretical: 47.89 (C%), 4.52 (H%), 13.96 (N%), 17.67(Cl%); Found: 48.26 (C%), 4.66 (H%), 13.52 (N%), 16.94 (Cl%)

MP: 88-90°C



methyl 2-(4-nitrophenyl)hydrazinecarboxylate

Color and State: Yellow solid

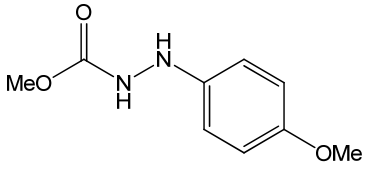
^{1}H NMR (400 MHz, DMSO) δ 3.62 (s, 3H), 6.75-6.73 (d, 2H), 8.07-8.05 (d, 2H), 8.99 (s, broad 1H), 9.44 (s, broad 1H).

^{13}C NMR (400 MHz, DMSO) δ 157.78, 147.94, 129.28, 121.06, 113.10, 52.98.

MS (EI+, [M]+) $C_8H_9N_3O_4$ 211, found 212.

MP: 176-178°C

EA Theoretical: 45.50 (C%), 4.30 (H%), 19.90 (N%); Found: 45.71 (C%), 4.48 (H%), 19.82 (N%)



methyl 2-(4-methoxyphenyl)hydrazinecarboxylate

Color and State: Orange solid

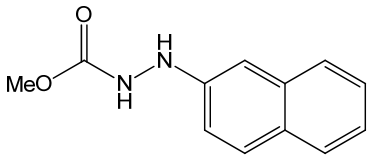
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 3H), 3.74 (s, 3H), 6.79 (s, Broad 4H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 157.88, 154.58, 141.67, 126.69, 114.64, 55.71, 52.94.

MS (EI+, [M]+) $C_9H_{12}N_2O_3$ 196, found196.

MP: 98-100°C

EA Theoretical: 55.09 (C%), 6.16 (H%), 14.28 (N%); Found: 54.98.03 (C%), 6.20 (H%), 14.08 (N%)



methyl 2-(naphthalen-2-yl)hydrazinecarboxylate

Color and State: Yellow solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 6.52 (s, broad 1H), 6.92 (s,

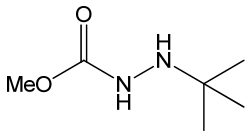
Broad 1H), 7.74-7.34 (m, 4H), 7.78-7.85 (m, 3H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 157.76, 142.63, 134.17, 132.55, 128.58, 126.27, 126.05, 125.79, 125.53, 121.14, 119.99, 53.02.

MS (EI+, [M]+) $C_{12}H_{12}N_2O_2$ 216, found 217.

MP: 104-106°C

EA Theoretical: 66.65 (C%), 5.59 (H%), 12.96 (N%); Found: 65.92 (C%), 5.63 (H%), 12.57 (N%)



methyl 2-(tert-butyl)hydrazinecarboxylate

Color and State: Colorless solid

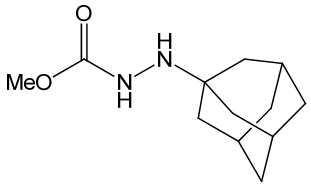
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (s, 9H), 3.64 (s, 3H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 158.41, 54.72, 52.34, 26.84.

MS (EI+, [M]+) $C_6H_{14}N_2O_2$ 146, found 147.

MP: 48-50°C

EA Theoretical: 49.30 (C%), 9.65 (H%), 19.16 (N%); Found: 49.92 (C%), 9.45 (H%), 20.16 (N%)



methyl 2-((1s,3s)-adamantan-1-yl)hydrazinecarboxylate

Color and State: White solid

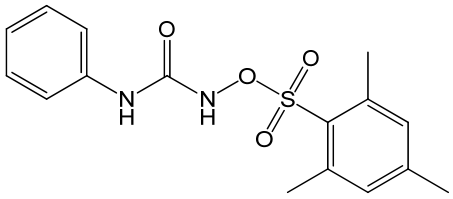
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60-1.57 (m, 11H), 2.03 (m, 6H) 3.66 (s, 3H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 158.62, 54.92, 52.49, 40.71, 36.59, 29.38.

MS (EI+, [M]+) $C_{10}H_{20}N_2O_2$ 224, found 225.

MP: 204-206°C

EA Theoretical: 64.26 (C%), 8.99 (H%), 12.49 (N%); Found: 63.98 (C%), 8.44 (H%), 12.68 (N%)



1-((mesitylsulfonyl)oxy)-3-phenylurea

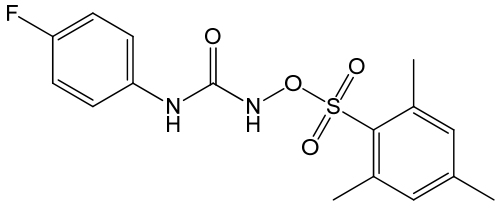
Color and State: White solid

^{1}H NMR (400 MHz, DMSO) δ 2.26 (s, 3H), 2.61 (s, 6H), 6.99-6.79 (t, 2H), 7.09 (s, 2H), 7.24-7.20 (t, 2H), 7.42-7.40 (d, 2H), 9.23 (s, 1H), 10.55 (s, 1H).

^{13}C NMR (400 MHz, DMSO) δ 155.41, 144.05, 140.80, 138.50, 131.59, 128.92, 128.69, 122.91, 119.20, 22.39, 20.59.

MS (EI+, [M]+) $C_{16}H_{18}N_2O_4S$ 334, found 334.

M.P.: 168-170°C (decomp.)



1-(4-fluorophenyl)-3-((mesitylsulfonyl)oxy)urea

Color and State: White solid

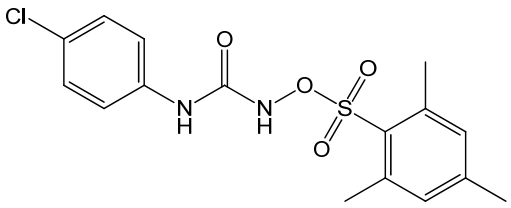
^{1}H NMR (400 MHz, DMSO) δ 2.26 (s, 3H), 2.61 (s, 6H), 7.10-7.06 (dd, 2H), 7.09 (s, 2H), 7.46-7.42 (dd, 2H), 9.33 (s, 1H), 10.59 (s, 1H).

^{13}C NMR (400 MHz, DMSO) δ 159.13, 155.57, 144.06, 140.81, 131.59, 128.92, 121.13, 115.34, 115.12, 22.38, 20.57.

MS (EI+, [M]+) $C_{16}H_{17}FN_2O_4S$ 352, found 353.

M.P.: 162-164°C (decomp.)

EA Theoretical: 54.54 (C%), 4.86 (H%), 7.95 (N%), 5.39 (F%), 9.10 (S%); Found: 54.29 (C%), 4.96 (H%), 7.82 (N%), 5.24 (F%), 9.08 (S%)



1-(4-chlorophenyl)-3-((mesitylsulfonyl)oxy)urea

Color and State: White solid

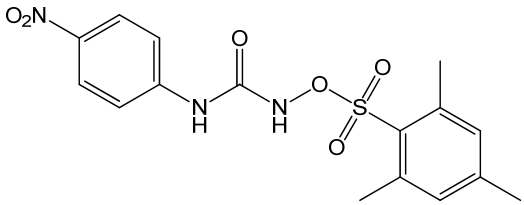
^{1}H NMR (400 MHz, DMSO) δ 2.26 (s, 3H), 2.61 (s, 6H), 7.09 (s, 2H), 7.27-7.25 (t, 2H), 7.45-7.43 (d, 2H), 9.42 (s, 1H), 10.64 (s, 1H).

^{13}C NMR (400 MHz, DMSO) δ 155.38, 144.07, 140.79, 137.53, 131.58, 128.84, 128.56, 126.53, 120.67, 22.36, 20.57.

MS (EI+, [M]+) $C_{16}H_{17}ClN_2O_4S$ 380, found 380.

M.P.: 172-174°C (decomp.)

EA Theoretical: 52.10 (C%), 4.65 (H%), 7.60 (N%), 9.61 (Cl%), 8.69 (S%); Found: 52.07 (C%), 4.57 (H%), 7.44 (N%), 9.42 (Cl%), 8.61 (S%)



1-(4-nitrophenyl)-3-((mesitylsulfonyl)oxy)urea

Color and State: Pale Yellow solid

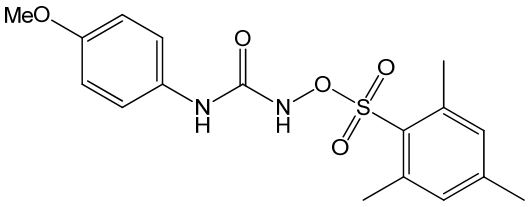
^{1}H NMR (400 MHz, DMSO) δ 2.23 (s, 3H), 2.60 (s, 6H), 7.07 (s, 2H), 7.67-7.64 (d, 2H), 8.14-8.12 (d, 2H), 10.00 (s, 1H), 10.98 (s, 1H).

^{13}C NMR (400 MHz, DMSO) δ 155.23, 145.22, 144.24, 141.85, 140.90, 131.65, 128.69, 124.96, 118.42, 22.42, 20.59.

MS (EI+, [M]+) $C_{16}H_{17}N_3O_6S$ 379, found 379.

M.P.: 194-196°C (decomp.)

EA Theoretical: 50.65 (C%), 4.52 (H%), 11.08 (N%), 8.45 (S%); Found: 50.37 (C%), 4.62 (H%), 11.00 (N%), 8.51 (S%)



1-(4-methoxyphenyl)-3-((mesitylsulfonyl)oxy)urea

Color and State: White solid

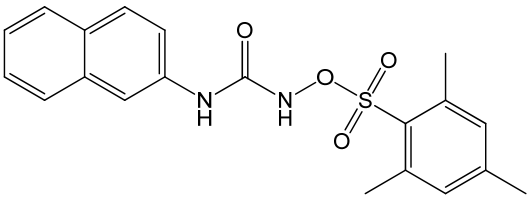
^{1}H NMR (400 MHz, DMSO) δ 2.26 (s, 3H), 2.61 (s, 6H), 3.68 (s, 3H), 6.83-6.81 (d, 2H), 7.09 (s, 2H), 7.33-7.31 (d, 2H), 9.08 (s, 1H), 10.45 (s, 1H).

^{13}C NMR (400 MHz, DMSO) δ 155.57, 155.19, 144.02, 140.79, 131.58, 131.38, 128.98, 122.12, 113.84, 55.16, 22.39, 20.58.

MS (EI+, [M]+) $C_{17}H_{20}N_2O_5S$ 364, found 364.

M.P.: 166-168°C (decomp.)

EA Theoretical: 56.03 (C%), 5.53 (H%), 7.69 (N%), 8.80 (S%); Found: 56.08 (C%), 5.58 (H%), 7.74 (N%), 8.85(S%)



1-((mesitylsulfonyl)oxy)-3-(naphthalen-2-yl)urea

Color and State: Pale Orange solid

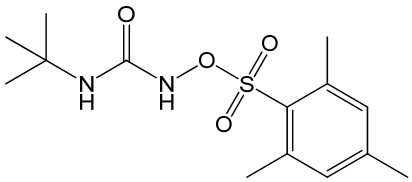
^{1}H NMR (400 MHz, DMSO) δ 2.30 (s, 3H), 2.65 (s, 6H), 7.15 (s, 2H), 7.52-7.44 (m, 4H), 7.75-7.74 (m, 2H), 7.91-7.89 (d, 1H).

^{13}C NMR (400 MHz, DMSO) δ 156.45, 144.13, 140.97, 133.77, 132.99, 131.63, 129.91, 128.84, 128.54, 128.06, 126.04, 125.82, 125.55, 122.61, 122.28, 22.49, 20.63.

MS (EI+, [M]+) $C_{20}H_{20}N_2O_4S$ 384, found 384.

M.P.: 164-166°C (decomp.)

EA Theoretical: 62.48 (C%), 5.24 (H%), 7.29 (N%), 8.34(S%); Found: 62.48 (C%), 5.30 (H%), 7.19 (N%), 8.29 (S%)



1-(tert-butyl)-3-((mesitylsulfonyl)oxy)urea

Color and State: White solid

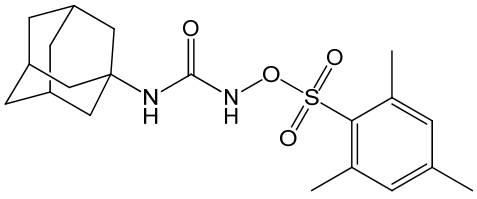
^{1}H NMR (400 MHz, DMSO) δ 1.10 (s, 9H), 2.25 (s, 3H), 2.54 (s, 6H), 5.98 (s, 1H), 7.08 (s, 2H), 9.96 (s, 1H).

^{13}C NMR (400 MHz, DMSO) δ 156.37, 144.13, 140.75, 131.64, 128.74, 50.22, 28.44, 22.56, 20.59.

MS (EI+, [M]+) $C_{14}H_{22}N_2O_4S$ 314 found 314.

M.P.: 146-148°C

EA Theoretical: 53.48 (C%), 7.05 (H%), 8.91 (N%), 10.20 (S%); Found: 53.59 (C%), 6.93 (H%), 8.96 (N%), 10.26 (S%)



1-((3s,5s,7s)-adamantan-1-yl)-3-((mesitylsulfonyl)oxy)urea

Color and State: White solid

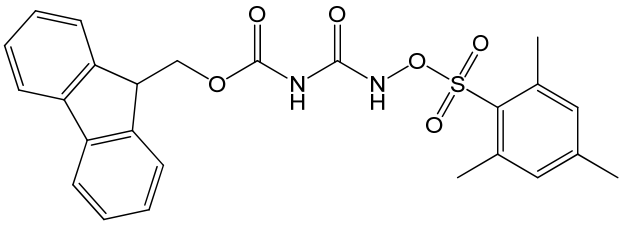
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (s, 6H), 1.91-1.90 (d, 6H), 2.07 (m, 3H), 2.33 (s, 3H), 2.63 (s, 3H), 5.42 (s, 1H), 7.01 (s, 2H), 7.24 (s, 1H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 156.53, 153.40, 144.87, 141.46, 132.17, 52.06, 41.58, 36.31, 29.52, 23.12, 21.30.

MS (EI+, [M]+) $C_{20}H_{28}N_2O_4S$ 392, found 392.

M.P.: 166-168°C

EA Theoretical: 61.20 (C%), 7.19 (H%), 7.14 (N%), 8.17 (S%); Found: 61.25 (C%), 7.07 (H%), 7.12 (N%), 8.20 (S%)



1-(fmoc)-3-((mesitylsulfonyl)oxy)urea

Color and State: White solid

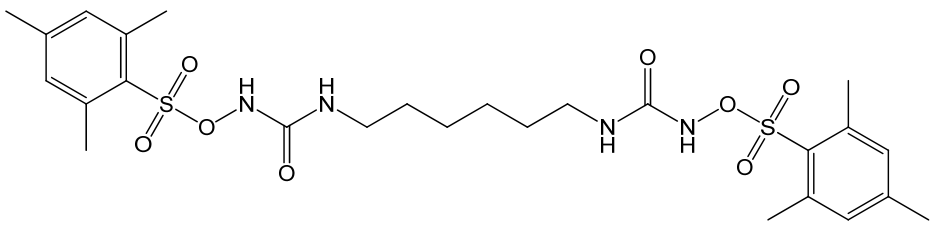
^{1}H NMR (400 MHz, DMSO) δ 2.29 (s, 3H), 2.59 (s, 6H), 4.23 (m,1H), 4.33 (m, 2H), 7.11 (s, 2H), 7.32 (t, 2H), 7.40 (t, 2H), 7.71 (d, 2H), 7.90 (d, 2H), 10.60 (s, 1H), 11.20 (s, 1H).

^{13}C NMR (400 MHz, DMSO) δ 153.01, 151.91, 144.31, 143.33, 141.17, 140.74, 131.55, 127.94, 127.84, 127.17, 125.35, 120.22, 66.90, 46.09, 22.45, 20.64.

MS (ESI+, [M]+) $C_{25}H_{24}N_2O_6S$ 480, found 481.

M.P.: 184-186°C (decomp.)

EA Theoretical: 62.49 (C%), 5.03 (H%), 5.83 (N%), 6.67 (S%); Found: 62.25 (C%), 5.06 (H%), 5.83 (N%), 6.61 (S%)



1,1'-(hexane-1,6-diyl)bis(3-((mesitylsulfonyl)oxy)urea)

Color and State: White solid

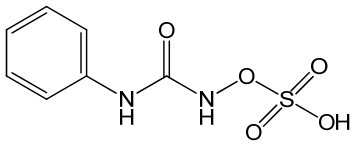
^{1}H NMR (400 MHz, DMSO) δ 1.11 (m, 2H), 1.29 (m, 2H), 2.27 (s, 3H), 2.54 (s, 6H), 2.96 (m, 2H), 7.10 (s, 2H).

^{13}C NMR (400 MHz, DMSO) δ 157.93, 144.00, 140.80, 131.62, 129.06, 48.70, 24.90, 25.89, 22.43, 20.60.

MS (ESI+, [M]+) $C_{26}H_{38}N_4O_8S_2$ 598, found 599.

M.P.: 180-182°C

EA Theoretical: 52.16 (C%), 6.40 (H%), 9.36 (N%), 10.71 (S%); Found: 52.04 (C%), 6.38 (H%), 9.41 (N%), 10.64 (S%)

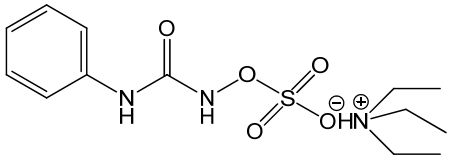


((3-phenylureido)oxy)sulfonic acid

Color and State: White solid

^{1}H NMR (400 MHz, DMSO) δ 7.34-7.28 (m, 3H), 7.46-7.42 (t, 2H), 8.45 (s, 1H).

^{13}C NMR (400 MHz, DMSO) δ 157.00, 133.23, 130.93, 127.44, 122.60.

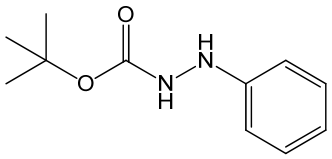


triethylammonium 3-phenylureido sulfate

Color and State: yellow oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28-1.17 (t, 9H), 3.11-3.04 (q, 6H), 7.01-6.97 (t, 1H), 7.22-7.18 (t, 2H), 7.42-7.40 (d, 2H), 8.27 (s broad, 2H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 157.73, 137.71, 128.88, 123.74, 119.27, 46.77, 8.69.



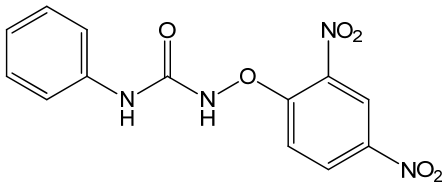
tert-butyl-2-phenylhydrazinecarboxylate

Color and State: White solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46(s, 9H), 5.88 (broad s, 1H), 6.62 (broad, 1H), 6.78-6.80 (d, 2H) 6.85-6.88 (t, 1H), 7.19-7.23 (t, 2H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 156.44, 148.45, 129.17, 120.74, 113.02, 81.23, 28.31

HRMS ($C_{11}H_{16}N_2O_2$) Exact Mass Calculated: 208.1204 Found: 208.1212



1-(2,4-dinitrophenoxy)-3-phenylurea

Color and State: Yellow solid

^{1}H NMR (400 MHz, DMSO) δ 7.16-7.19, (t, 1H),7.34-7.38, (t, 2H), 7.50-7.52 (d, 2H), 7.59-7.61 (s, 1H), 8.45-8.48 (dd, 1H), 8.82 (d, 1H).

^{13}C NMR (400 MHz, DMSO) δ 155.69, 150.75, 143.27, 136.17, 129.41, 129.13, 125.46, 120.36, 117.26.

MS (ESI+, [M]+) $C_{13}H_{10}N_4O_6$ 318.24, found: 318.0.

CHAPTER 2: SYNTHESIS OF CARBAMOYL AZIDES FROM AMINES USING CO_2 AT AMBIENT CONDITIONS

2.1 Carbamoyl Azide Overview

2.1.1 Carbamoyl Azide Importance

Carbamoyl azides have been prepared and studied for over a century, but their use in synthesis is relatively rare. [45] The most famous example of carbamoyl azide use is an intermediate step in the synthesis of the fat metabolism regulator (+)-biotin (Fig. 2.1). [46, 47]

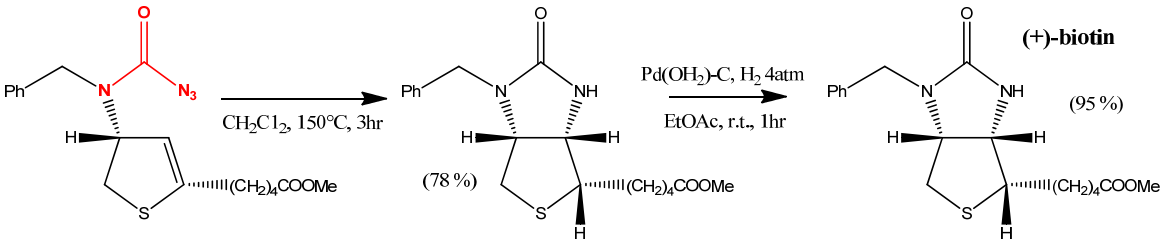


Figure 2.1: Synthesis of (+)-biotin from a carbamoyl azide intermediate.

Other examples of their use in literature include: formation of antineoplastic cysteamines [48], thermolysis to indazoles [49-51], synthesis of substituted ureas [52], use as an aminating agent [53], foaming agent in polyolefins [54], and photolysis to hydrazine carboxylates. [31, 33] A few of these examples of carbamoyl azide use are outlined in fig. 2.2.

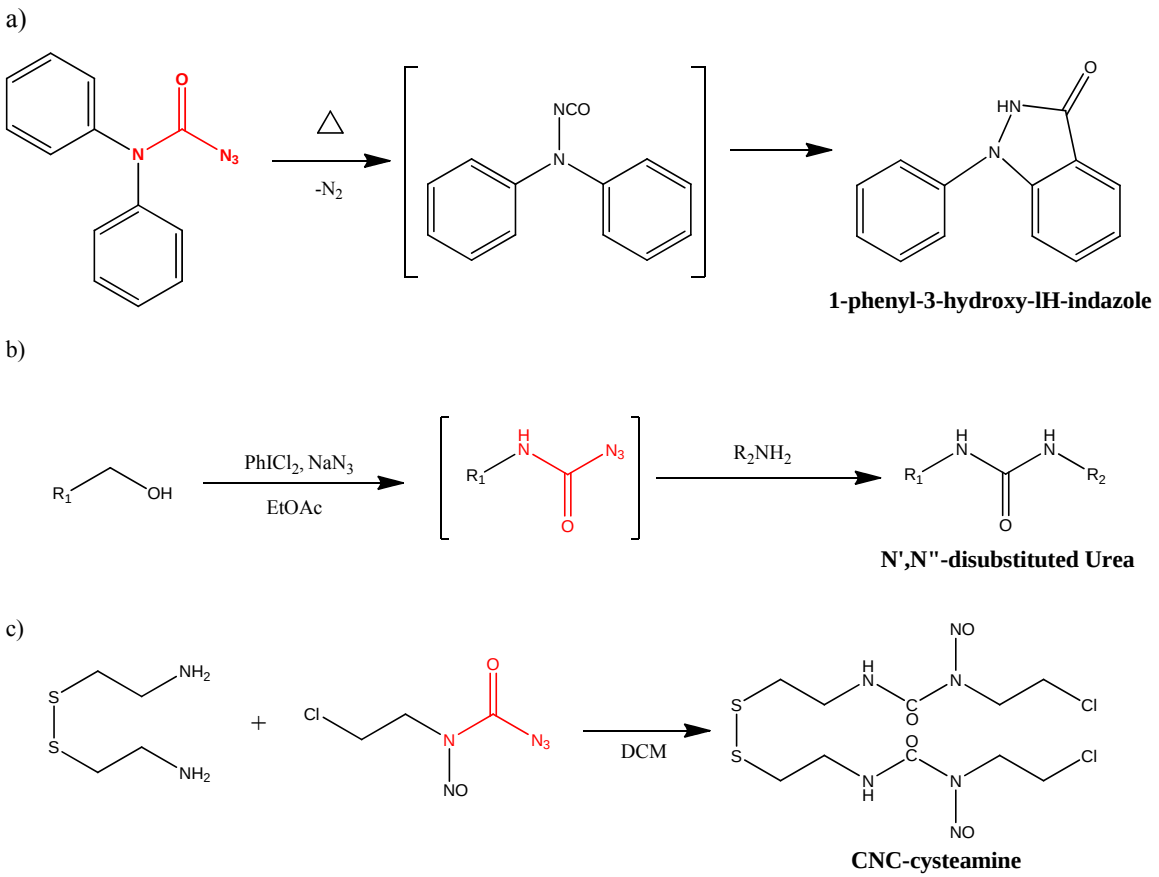


Figure 2.2: a) Curtius synthesis of 1-phenyl-3-hydroxyl-1H-indazole. b) Synthesis of N',N"-disubstituted urea. c) Synthesis of antineoplastic CNC-cystamine

2.1.2 Synthesis of Carbamoyl Azides in Literature

Carbamoyl azides belong to a class of compounds which usually require the use of hazardous reactants and corrosive conditions as standard procedures for synthesis. In the past, the most popular method of synthesis was the reaction of isocyanates with hydrazoic acid (Fig. 2.3). [55-57]

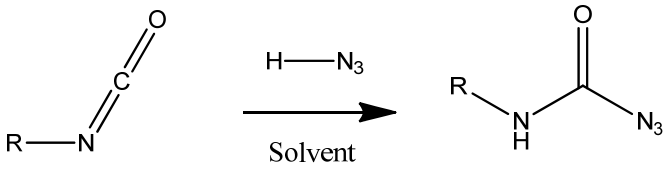
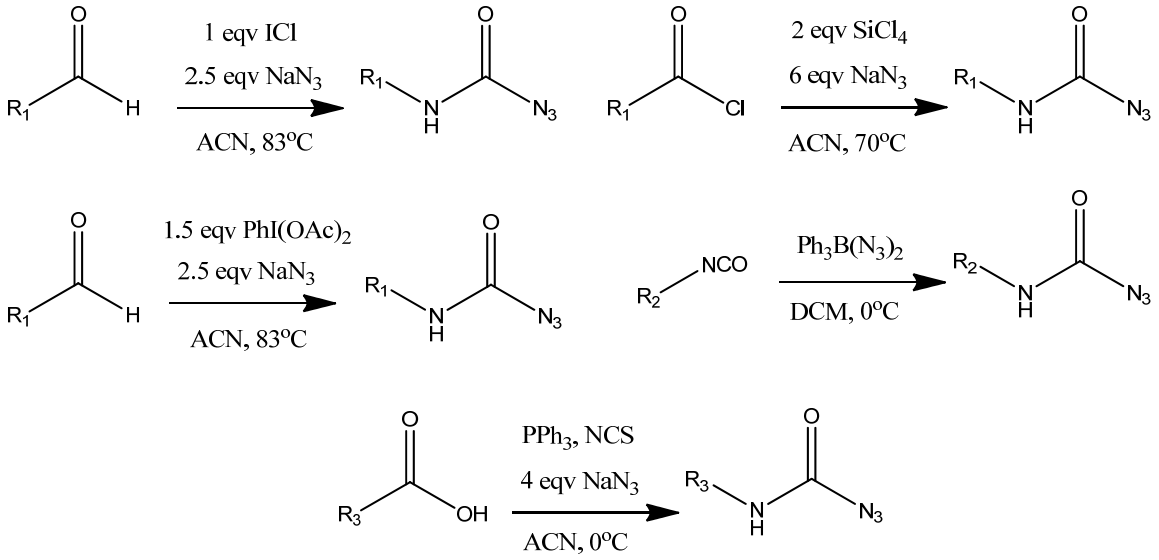


Figure 2.3: General reaction of isocyanates with hydrazoic acid to form carbamoyl azides

However, hydrazoic acid is extremely explosive when there is a slight input of external energy. [58, 59] It is therefore advantageous to develop alternative pathways for the production of these carbamoyl azides that do not suffer from these downfalls. Recently, many papers have studied new routes to the formation of carbamoyl azides, such as, the radical reaction of aldehydes with iodine monochloride [60] or iodosobenzene diacetate [61], acid chlorides with silicon tetrachloride [62], carbonic hydrides with potassium monophosphate [63], carboxylic acids with triphenylphosphine/succinimide [64] or bis(2-methoxyethyl)aminosulfur trifluoride [65] or isocyanates with triarylbismuth diazides. [66] Figure 2.4 shows representations of some these reactions.



R_1= Alkyl and Aryl, R_2= Aryl Only, R_3= Alkyl Only

Figure 2.4: Examples of recent syntheses of carbamoyl azides

However, despite avoiding the use of hydrazoic acid, these methods still suffer from drawbacks that make them undesirable for many syntheses, such as expensive starting materials, corrosive conditions, high temperatures which are energy intensive and a lack of generality (only applicable to an alkyl or aryl species). In light of this, a more benign and energy friendly synthetic route for the production of carbamoyl azides incorporating amines, a base and carbon dioxide was developed.

2.2 Synthesis Methods with Amines, CO_2 and Base

2.2.1 Previous Reactions with CO_2 and Amines

Reactions involving amines and CO_2 in the presence of base have previously been studied and have recently gained popularity in synthesizing many compounds such as carbamates [67], cyanoformamides [68], and ureas [69] to name a few (Fig. 2.5).

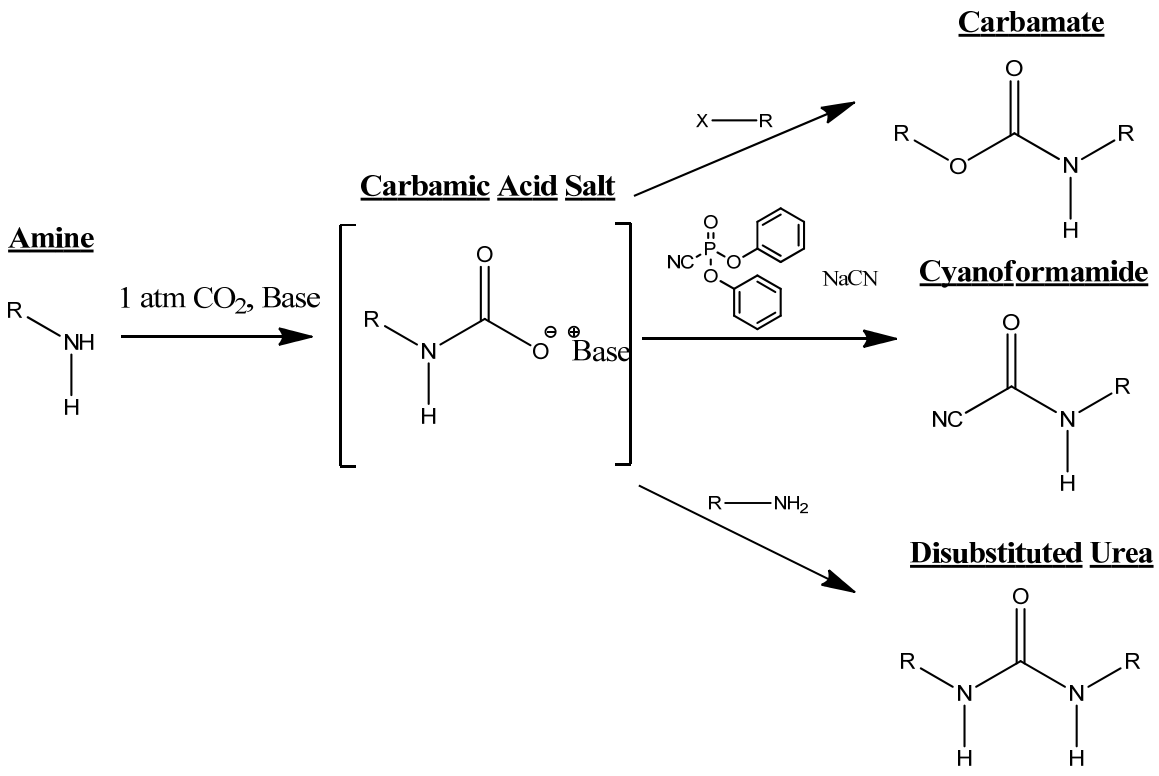


Figure 2.5: Examples of reactions of amines with CO_2 in the presence of base

The proposed mechanism involves the reaction of an amine with CO_2 with a base to make a carbamic acid salt. The subsequent carbamic anion can then react directly with a halide in a S_N2 reaction to form carbamates or react with phosphoryls to make the O atom a good leaving group, which can be displaced a number of nucleophiles.

2.2.2 Prior Synthesis of Alkyl Carbamoyl Azides with CO_2, PhTMG, and DPPA

Building upon the examples mentioned above, a 2007 study by Garcia-Guido et. al. showed the conversion of amines to carbamoyl azides in good yield (69-90%) using carbon dioxide (CO_2), tetramethylphenylguanidine (PhTMG) as the base, and diphenylphosphoryl azide (DPPA) (Fig. 2.6). [70]

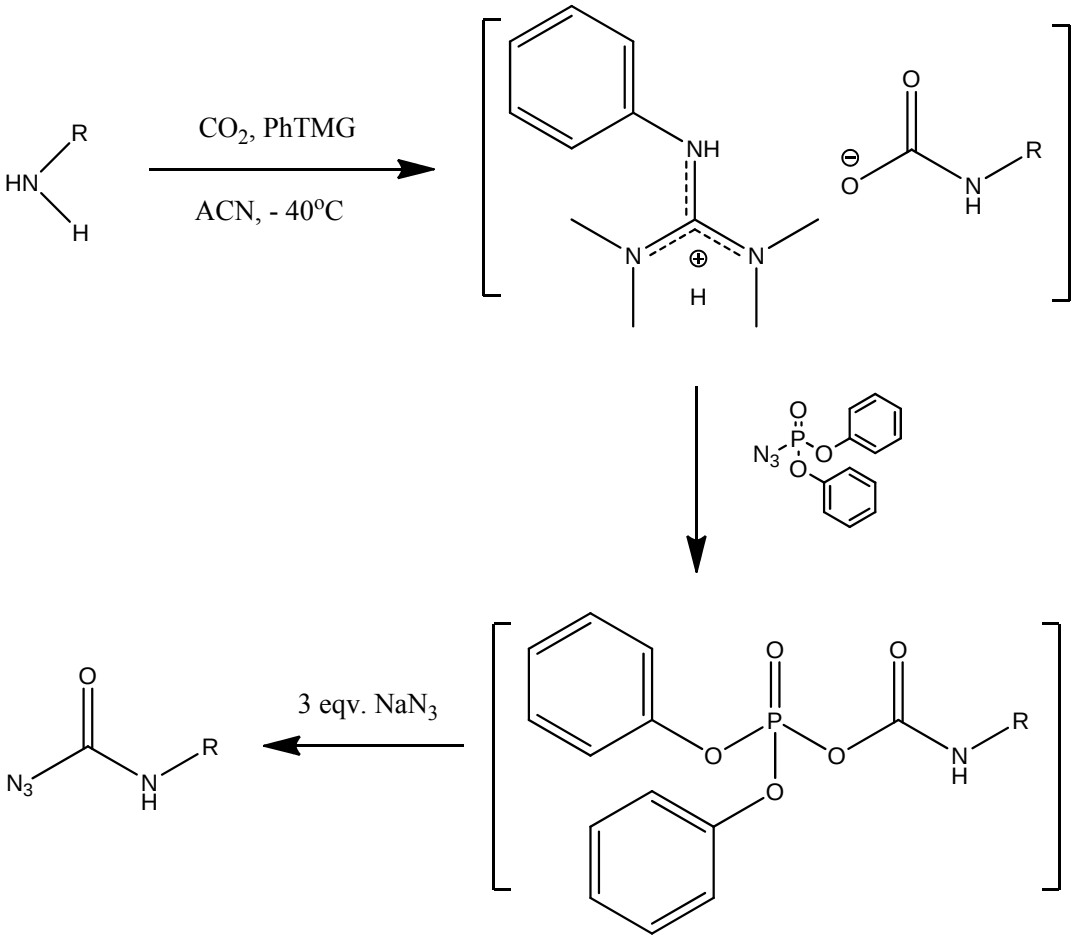


Figure 2.6: Synthesis of alkyl carbamoyl azides using CO_2, PhTMG, NaN_3 and DPPA

This groundbreaking work opened the door for a facile synthesis to carbamoyl azides without the use of harsh reagents and undesirable reaction conditions seen in the

traditional methods. Garcia-Guido et. al. was also the first to demonstrate the synthesis of dialkyl substituted carbamoyl azide, but the reaction had to be modified from their previous work. Dibutylamine, when reacted with CO_2, DPPA and TMPG at 0°C, forms a stable phosphoric anhydride (Fig. 2.7). When the reaction was heated to 60°C in acetonitrile for several hours with NaN_3, they were able to obtain dibutyl carbamoyl azide in moderate yields (53%).

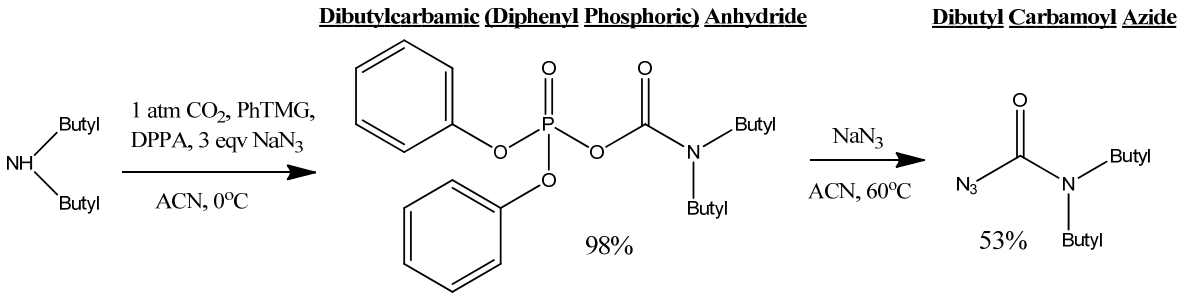


Figure 2.7: Synthesis of dibutyl carbamoyl azide from dibutylamine

However, despite being novel, these studies can be improved upon. Firstly, the carbamoyl azides studied by Garcia-Guido et. al. were limited to only alkyl substituted examples; no aryl examples were presented. Secondly, the extremely cold (-40°C) or reflux (60C°) temperatures used are not suitable for larger scale production of the desired products and only add to the energy input. Ideally these reactions can be improved on through the use of ambient temperatures (0°C-25°C). Lastly the base, PhTMG, is not commercially available for use.

2.2.3 Synthesis of PhTMG

Both works employ the use of guanidines (like PhTMG), which are considered ideal due to the stabilization of the carbamate anion by the guanidinium cation since the anions are only weakly solvated by the solvent[71]. Guanidiniums are also highly stable, because of the delocalization of the positive charge when protonated (Fig. 2.8).

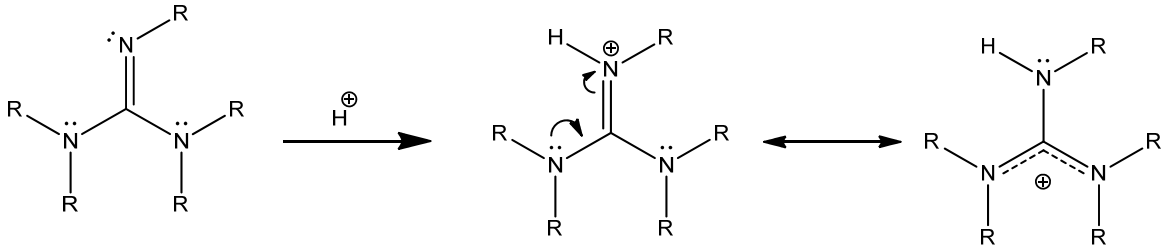


Figure 2.8: Protonation of gaunidine to a stable guanidinium

PhTMG can be used successfully in acetonitrile (some guanidines are not soluble in organics), so it was attractive to use in the synthesis of carbamoyl azides. However, PhTMG is not readily available for purchase and must be synthesized via a reaction with aniline and tetramethylurea in the presence of phosphoryl chloride ($POCl_3$) (Fig. 2.9). [72]

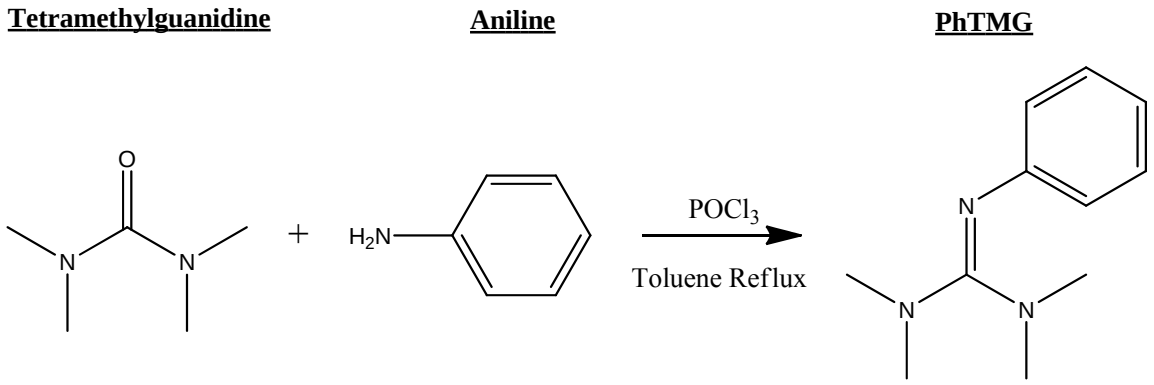


Figure 2.9: Synthesis of PhTMG with aniline, tetramethylurea and $POCl_3$

For this reaction to be more attractive for the synthesis of carbamoyl azides, it would be beneficial to find a commercially available base to replace PhTMG.

2.2.4 CO_2 Protection of Benzylamine

One such commercially available base that has been shown to stabilize both alkyl and aryl carbamic anions is 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). In some studies, carbamate/DBU salts were characterized as a stable species. [73, 74] A scheme showing the stabilization of the benzyl carbmaic acid with DBU is shown in Fig. 2.10.

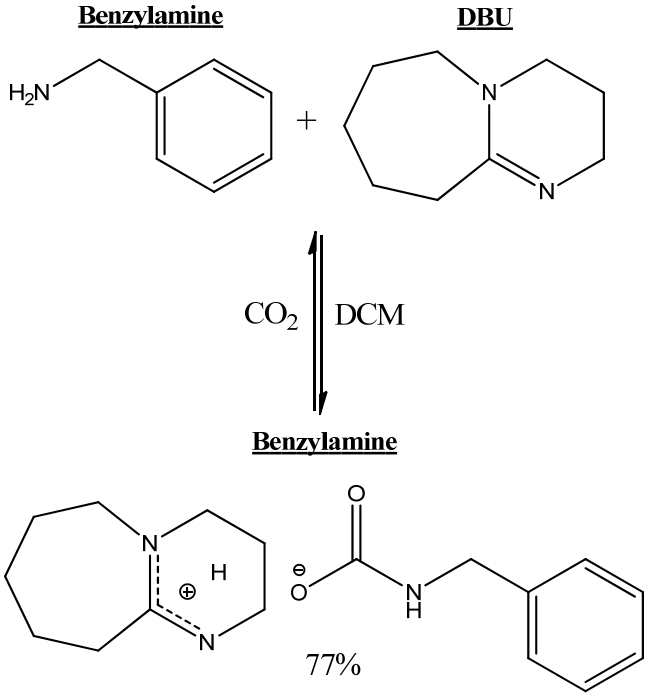


Figure 2.10: CO_2 protected benzylamine as a carbamic salt with DBU base [74]

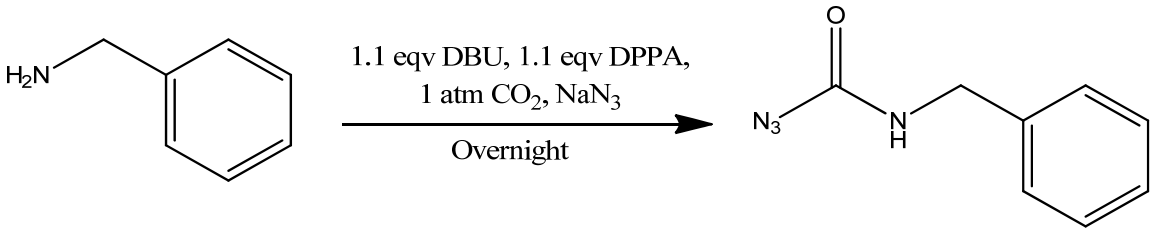
Since DBU shows promise as a suitable replacement for the PhTMG, this chapter investigates the application of DBU and ambient conditions (0°C-20°C) in the synthesis of carbamoyl azides.

2.3 Synthesis of Carbamoyl from Amines using CO_2, DBU, and DPPA

2.3.1 Synthesis of Benzyl Carbamoyl Azide and Optimization

DBU was initially screened as a suitable base for the synthesis of carbamoyl azides from benzyl amine by varying the temperature, solvent, and sodium azide equivalent (Table 2.1).

Table 2.1: Reaction of benzylamine with CO_2, DBU, DPPA and NaN_3 at varying temperatures, azide equivalents, and solvent



Trial	Temp (C°)	NaN_3 eqv.	Solvent	Isolated Yield (%)
1	RT	3	AcCN (20 mL)	74
2	RT	3	DMF (10 mL)	76
3	0	3	DMF (10 mL)	89

4	0	2	DMF (10 mL)	83
5	0	1	DMF (10 mL)	76

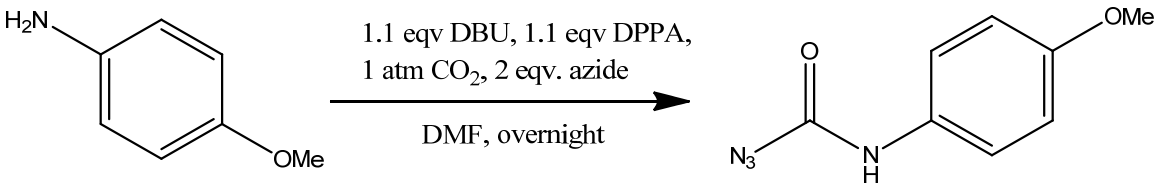
Acetonitrile required twice the amount of volume due to its evaporation during the sparging of CO_2. DMF, with a high boiling point, could be used with continuous CO_2 flow without a gradual decrease in volume and did not pose a separation problem during work up. Both yielded similar values (Table 2.1, Trial 1 and 2), 74% (AcCN) and 76% (DMF), but DMF is advantageous since it did not evaporate. Temperature had a significant effect as reactions at 0°C had higher yields than at room temperature (RT). Increasing to 3 equivalents of NaN_3 (Table 2.1, Trial 3) performed only slightly better (6% better) than 2 equivalents (Table 2.1, Trial 4) at 0°C in DMF. However, reducing the number of equivalents of an azide would be quite beneficial from a safety standpoint as azides can be explosive and one should take the decrease in yield vs. the inherent dangers into consideration. The experimental data also shows that a temperature of 0°C (Table 2.1, Trial 3) is favored over room temperatures (Table 2.1, Trial 2), with the yield increased by 13% more for 0°C. Overall, we found that the optimum conditions for the synthesis of benzyl carbamoyl azide consists of dimethylformamide (DMF) as the solvent, a 0°C temperature, and 2 equivalents of NaN_3.

2.3.2 Synthesis of *p*-Methoxyphenyl Carbamoyl Azide and Optimization

The synthesis of *p*-methoxyphenylcarbamoyl azide from *p*-methoxyphenylamine using the modified procedure was also shown to be successful. The effect of temperature and

type of metal azide was investigated for this reaction (Table 2.2).

Table 2.2 Reaction of *p*-methoxy aniline with CO_2, DBU, DPPA and metal azide at varying temperatures and differing metal azide.



Temp (C°)	Metal Azide	Yield (%)
RT	NaN_3	38
RT	CsN_3	79
0	NaN_3	76

The effect of temperature on this reaction followed a similar trend to the benzyl amine reactions. As the temperature is decreased from RT to 0°C, the yield increases from 38% to 76%, respectively. This is quite a substantial change compared to the benzylamine example. But the most interesting development was certainly the improved performance of the reaction with CsN_3 at the higher temperature. At room temperatures, the yield of *p*-methoxyphenyl carbamoyl azide was about two times greater than sodium azide. Salvatore et. al. reported similar results in studies they conducted with alcohol conversion to carboxyllic anhydrides using CO_2 and carbonate bases. [67] They showed that $CsCO_3$ gave them high yields while other alkali metals (Li, Na, K, and Rb) only produced the products in trace amounts. Clearly, the Cs^+ cation has a role in improving this reaction.

Salvatore et. al. attributed their improved results in carbamate synthesis using Cs_2CO_3 to the "cesium effect". [67] Other studies have shown that Cs^+ dramatically improved the direct alkylation of amines [75] and the ring closing reactions of aza-macrocycles. [76] One study found that Cs^+ salts had a twofold effect on intermolecular S_N2 substitutions: better solubility of the azide salt and a higher degree of dissociation into solvated cations and free anions. [77] Since the Cs^+ cation showed a noticeable increase in our reaction yields, we postulate that Cs^+ may coordinate with the carbamate anion before the phosphorylating agent reacts with the carbonyl oxygen (Fig. 2.11).

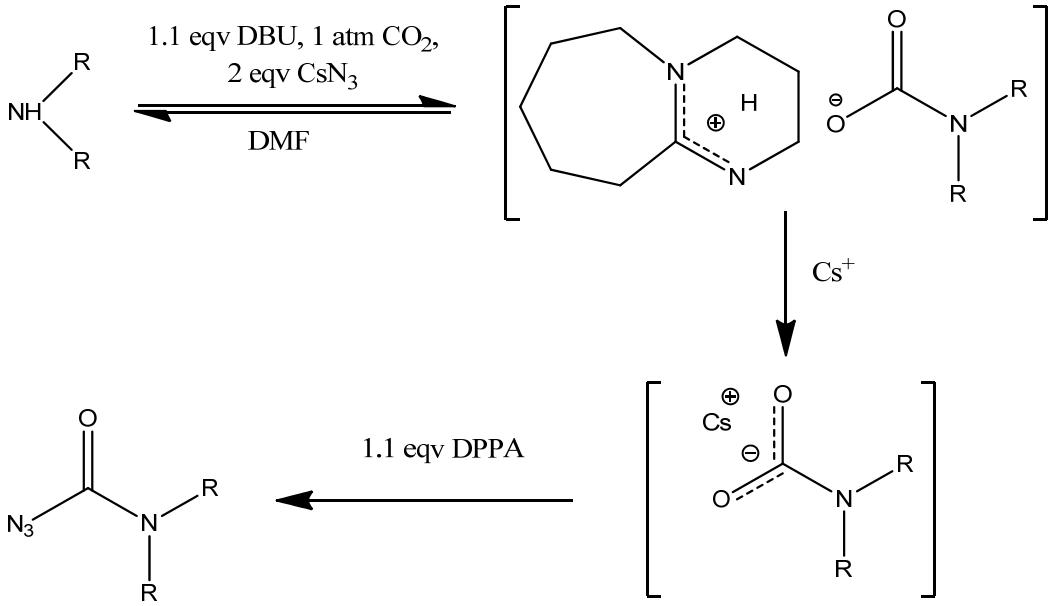


Figure 2.11: Amine to carbamoyl azide reaction with proposed cesium carbamate intermediate

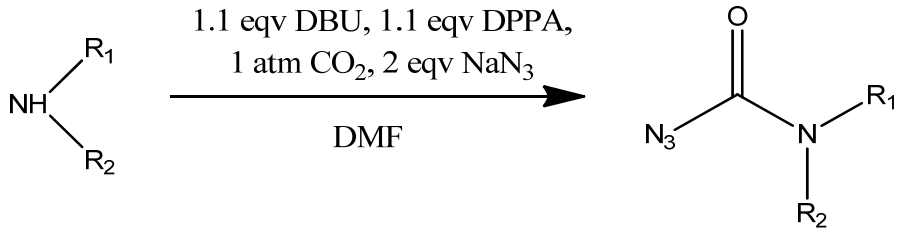
The Cs^+ cation can have two effects on the reaction: stabilization the carbamate anion (so it does not revert back to the amine and CO_2) and faster reaction with DPPA since the ions are more "naked" in solution. One disadvantage of using the higher yielding cesium

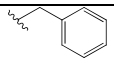
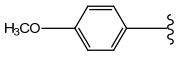
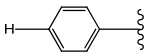
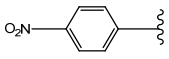
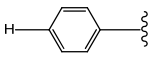
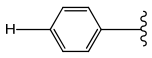
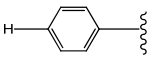
azide, however, may be its cost. Being significantly more expensive than sodium azide, we continued to use NaN_3 over CsN_3 whenever possible.

2.3.3 Synthesis of Various Mono- and Disubstituted Carbamoyl Azides with Sodium Azide

To study the generality of our reaction procedure, a range of mono- and disubstituted alkyl and aryl amines were reacted with CO_2, DBU, DPPA and NaN_3 (Table 2.3).

Table 2.3: Reaction of various monosubstituted and disubstituted amines with CO_2, DBU, DPPA and metal azides



Entry	R_1	R_2	Time (days)	Temp (°C)	Yield (%)
1		H-	1	0	83
2		H-	1	0	79
3		H-	1	0	68
4		H-	4	0	<10
5		CH_3-	4	0	0
6			4	0	0

7	$CH_3CH_2CH_2CH_2$-	H-	1	0	73
8	$NH_2CH_2CH_2CH_2CH_2CH_2CH_2$-	H-	1	0	53[a]
9	$CH_3CH_2CH_2CH_2$-	$CH_3CH_2CH_2CH_2$-	1	RT	56

a Compound contains 2 amines and formed 2 carbamoyl azide moieties in the product. 2.2 mol eqv of DBU, 2.2 mol eqv of DPPA and 4 eqv of NaN_3 were used in the reaction.

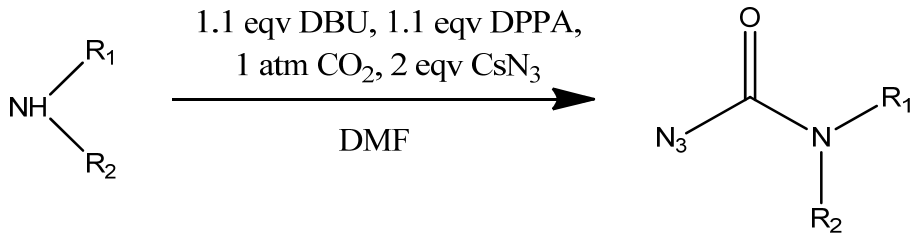
The aryl examples (Table 2.3, Entry 2-4) show a noticeable trend based on the electron effects of the para-substituents. The electron donating *p*-methoxy group had the highest yield (79%) of the aryl examples (Table 2.3, Entry 2), but the electron withdrawing *p*-nitro group did not yield any product (Table 2.3, Entry 4) with NaN_3. Electron donating groups, like *p*-methoxy, increase the amine's nucleophilicity and withdrawing groups, like p-nitro, decrease the nucleophilicity. In addition to the failure of the synthesis of *p*-nitrophenylcarbamoyl azide, both *N*-methylaniline and diphenylamine (Table 2.3, Entry 5-6) did not produce any carbamoyl azide product (only starting materials recovered), even after a prolonged period of time (4 days). Surprisingly, the reaction of dibutylamine with our conditions proceeded to the carbamoyl azide product (Table 2.3, 9) (56%) in a one pot instead of producing phosphoric anhydride that has occurred in previous research (Fig. 2.7). It should be noted that there are physical/mass transfer implications in the synthesis of butylcarbamoyl azide (Table 2.3, Entry 7) and hexyldicarbamoyl azide (Table 2.3, Entry 8). For these alkyl amine reactions (Entry 7-9), except Entry 1, a gel was produced upon CO_2 addition in the presence of DBU. This led to multiphase solutions which in turn caused the overall system to become more viscous. These problems create a mass transfer limitation to these reactions which may be the cause of

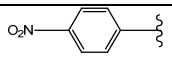
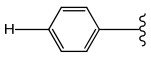
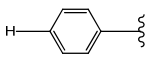
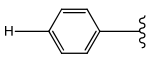
the lower yields. This characteristic was not seen in the synthesis of the benzylcarbamoyl azide.

2.3.4 Synthesis of Mono- and Disubstituted Carbamoyl Azides with Cesium Azide

According to Table 2.3, Entries 4, 5 and 6, the electron withdrawing groups decrease the nucleophilicity which results in the observed lowered yields of the azide. These reactions were repeated with the more reactive CsN_3 to see the "cesium effect" on the yield (Table 2.4).

Table 2.4: Reaction of various monosubstituted and disubstituted amines with CO_2, DBU, DPPA and cesium azide.



Entry	R_1	R_2	Time (days)	Temp (°C)	Yield (%)
4		H-	4	RT	31
5		CH_3-	4	RT	71
6			4	RT	<5[a]

[a] Crude Yield

Surprisingly, *p*-nitrophenylcarbamoyl azide and methylphenyl carbamoyl azide were synthesized in moderately yields (31% and 71%, respectively). There was some evidence

in ^{13}C NMR that a small amount diphenylcarbamoyl azide (<5%) was synthesized and a high resolution mass spectroscopy analysis confirmed the presence of the product. It was found that temperature did not play a factor in changing the yield (results not shown) even though reactions were ran for 4 days to reach completion.

2.4 Conclusions

In conclusion, the synthesis of both *N*-mono- and *N*-disubstituted aryl and akyl carbamoyl azides at ambient conditions (0°C-20°C) was demonstrated for the first time. Commercially available DBU was a successful base in these reactions, which can replace non-commercial organic guanidines. It was also found that CsN_3 is much more efficient than NaN_3 due to the "cesium effect" phenomenon and can be used to synthesize carbamoyl azides from amines with low nucleophilicity. The amines that did not react with NaN_3 to a carbamoyl azide were successful with CsN_3.

2.5 Recommendations

Even though the methods developed were improvements in the synthesis of carbamoyl azides, some of the yields and reaction times were substandard. It may be possible to obtain better yields and faster reactions with increased temperatures. None of the reactions studied were heated above room temperature. While heating may shift the equilibrium of the first reaction from carbamic salt to amine and CO_2 to some degree, the second step displacement reaction rate would be increased significantly. Since the second

reaction is irreversible, the first step would be rate limiting, the overall yield of the carbamoyl azide could improve given a longer period of time period of time.

2.6 Experimental

2.6.1 Synthesis Procedures

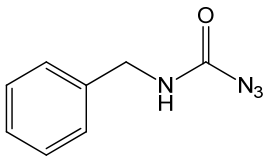
All solvents and reagents were purchased from commercial sources in reagent grade form and were used without further purification. Nuclear magnetic resonance (NMR) spectra were measured on a 400 MHZ Varian (1-D measurements). Mass spectrometry measurements were performed by electron impact (EI) or (ESI) on a micromass (Waters) autospec M. Infrared spectroscopy measurements were performed with neat samples on a Shimadzu FTIR prestige-21 equipped with a Specac golden gate ATR cell.

Procedure for the Synthesis of Carbamoyl Azides and Carbamic Phosphoric Anhydrides

To a 25 ml flask, 2.0 mmol of NaN_3 or CsN_3, 1 mmol of amine, and 10 ml of DMF was added and sparged with argon (the system was cooled to 0°C if NaN_3 was used). The flask is place in an ice-water bath and 1.1 mmol of DBU is added. The system is put under a 1 atm CO_2 atmosphere. After 3 hours, 1.1 mmol of DPPA is added and the solution is stirred for 1 or 4 days under CO_2. Upon completion, ethyl acetate and water are added to the reaction mixture and the organic layer separated in a separatory funnel. The organic layer is washed with water 2 times and a wash with 5% HCl solution. The

organic layer is separated, dried with $MgSO_4$, filtered and the solvent is evaporated under vacuum. The crude was purified using flash column chromatography (silica) with 9:1 hexane/ethyl acetate eluent.

2.6.2 Spectral Data



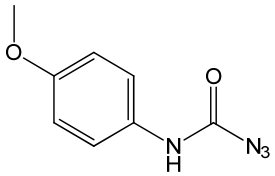
benzylcarbamoyl azide (1)

Color and State: White solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37-4.39 (d, 2H), 5.70 (broad s, 1H), 7.22-7.36 (m, 5H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 156.51, 137.18, 128.67, 127.70, 127.52, 44.92.

IR (Neat) 2145, (strong, N_3), 1675 (strong, C=O), 1555 (N-C=O).



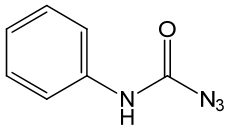
(4-methoxyphenyl)carbamoyl azide (2)

Color and State: White solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 6.82-6.85 (d, 2H), 7.32-7.34 (d, 2H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 156.64, 154.25, 136.69, 130.01, 121.34, 114.28, 55.49.

HRMS ($C_8H_8N_4O_2$) Exact Mass Calculated: 192.0650 Found: 192.0647



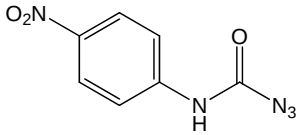
phenylcarbamoyl azide (3)

Color and State: White solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (broad s, 1H), 7.15-7.11 (t, 1H), 7.34-7.30 (t, 2H), 7.45-7.43 (d, 2H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 154.13, 136.69, 129.30, 124.77, 119.38.

IR (Neat) 2140, (strong, N_3), 1690 (strong, C=O), 1550 (N-C=O).



(4-nitrophenyl)carbamoyl azide (4)

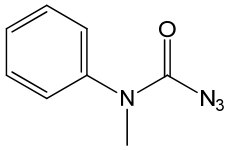
Color and State: Yellow solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.62-7.64 (d, 2H), 8.19-8.22 (d, 2H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 154.27, 143.75, 142.93, 125.80, 118.65.

IR (Neat) 2125(strong, N_3), 1680 (strong, C=O), 1500, 1335 (strong, N-O).

HRMS ($C_7H_5O_3N_5$) Exact Mass Calculated: 207.0390 Found: 207.0392



Methyl phenylcarbamoyl azide (5)

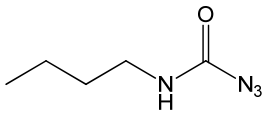
Color and State: Colorless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.32 (s, 3H), 7.19-7.41 (m, 5H)

^{13}C NMR (400 MHz, $CDCl_3$) δ 156.44, 142.38, 129.25, 127.75, 126.66, 38.36

IR (Neat) 2115 (strong, N_3), 1685 (strong, C=O)

HRMS ($C_8H_6ON_4$+H) Exact Mass Calculated: 177.0770 Found: 177.0771



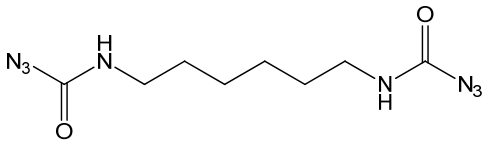
butylcarbamoyl azide (7)

Color and State: Colorless Oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88-0.92 (t, 3H), 1.29-1.37 (m, 2H), 1.44-1.51 (m, 2H), 3.19-3.24 (tt, 2H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 156.45, 40.85, 31.58, 19.86, 13.66.

IR (Neat) 3305(medium, N-H), 2135, (strong, N_3), 1685 (strong, C=O), 1530 (N-C=O)



hexane-1,6-diyldicarbamoyl azide (8)

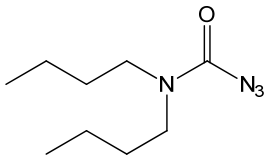
Color and State: White solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32-1.35 (m, 4H), 1.50-1.53 (m, 4H), 3.20-3.25 (t of t, 4H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 156.45, 40.74, 29.38, 25.95.

IR (Neat) 3320 (medium, N-H), 2145, (strong, N_3), 1680 (strong, C=O), 1535 (N-C=O).

HRMS ($C_8H_{14}O_2N_8$+Na) Exact Mass Calculated: 277.1132 Found: 277.1132



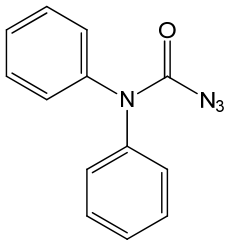
dibutylcarbamoyl azide (9)

Color and State: Colorless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90-0.94 (dd, 6H), 1.24-1.35 (m, 4H), 1.46-1.54 (m, 4H), 3.14-3.17 (t, 2H), 3.25-3.29 (t, 2H)

^{13}C NMR (400 MHz, $CDCl_3$) δ 156.35, 47.74, 47.13, 30.69, 29.82, 20.00, 19.86, 13.80, 13.75

HRMS ($C_9H_{18}ON_4$) Exact Mass Calculated: 198.1481 Found: 198.1482



dibutylcarbamoyl azide (6)

Un-isolated (<5% yield)

HRMS ($C_9H_{18}ON_4$) Exact Mass Calculated: 238.0858 Found: 238.0855

CHAPTER 3: WATER AT ELEVATED TEMPERATURES (WET): A REACTANT, CATALYST, AND SOLVENT IN THE SELECTIVE REMOVAL OF PROTECTING GROUPS

3.1 Water Deprotection Overview

3.1.1 Importance of Water to "Green" Chemistry

As the field of "green" chemistry has gained importance the last decade, the need to minimize the use of hazardous reagents has grown considerably. [78] More specifically, emphasis has been focused on environmentally friendly chemical processes incorporating inherently safer mediums such as water; an inexpensive, readily available and benign solvent. This has led to its use as a viable solvent medium for an array of organic reactions. [79-85]

3.1.2 Properties of Water at Elevated Temperature

Water can exist as a liquid at temperatures above 100°C when under pressurized conditions. The chemical and physical properties of liquid water at elevated temperatures (WET) above 100°C change drastically compared to common organic solvents. For example, the dielectric constant (ε) of water at 25°C decreases from ~79 to ~38 and finally ~19 as the temperature increases to 185°C and 300°C respectively (Fig. 3.1).

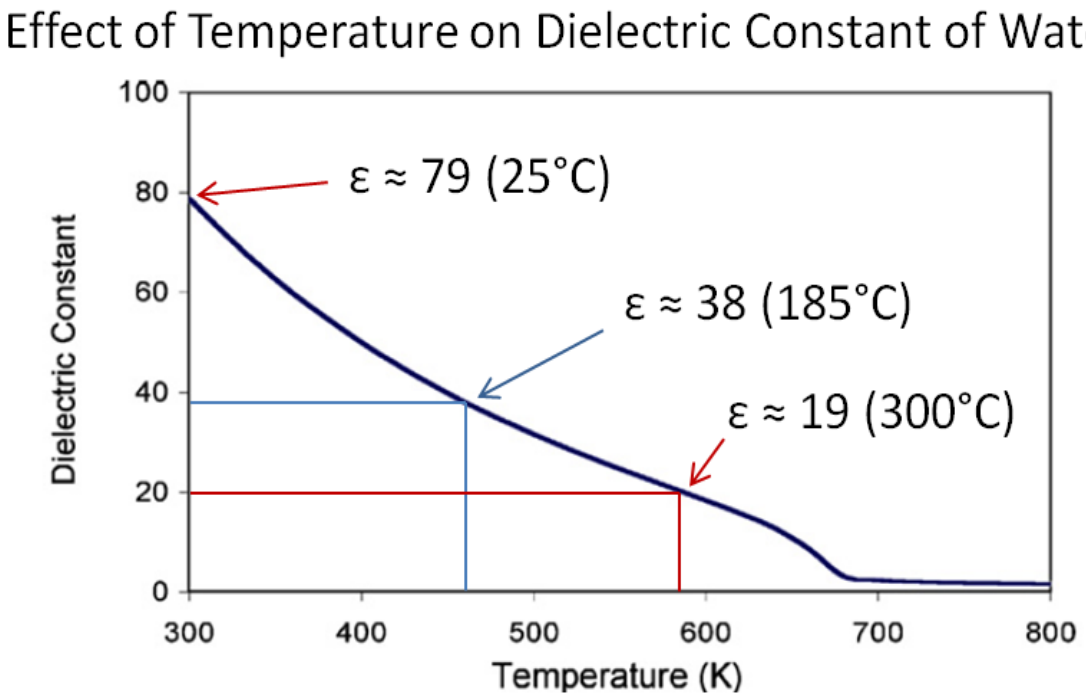


Figure 3.1: Dielectric constant of water as a function of temperature[86]

With a ε = 38, the solvent properties of water are similar to acetonitrile (ε=37.5) while a ε = 19 is equivalent to acetone (ε=20.7). Other changes in physical properties, like polarity and density, are attributed to the decrease in hydrogen bonding[87], which lowers the dielectric constant (ε) and enhances the solubility of nonpolar organic species. Also, the dissociation constant of water increases with temperature, leading to elevated levels of both hydronium (H^+) and hydroxide ions (OH^-). These dissociated water ions give the solvent the ability to act as a catalyst as well as a reactant with acid/base sensitive compounds. [88, 89] It is very important to recognize that the preceding phenomena of water can be tuned to meet specific solvent and reactivity needs by simply altering the temperature of the system. Furthermore, it may also be possible to achieve facile separation of the organic products from aqueous medium upon cooling from WET to

ambient conditions.

3.1.3 Deprotection Reactions in Synthesis

When a chemical reaction is to be carried out selectively at one reactive site in a multifunctional molecule, other potentially reactive sites or functional groups must be temporarily protected. An industry which uses these protection mechanisms includes the synthesis of pharmaceutical and natural products. These important compounds and intermediates rely heavily on the use of protecting groups due to the inherent complexity and multifunctional nature of the target molecule. [90, 91] In order for a protecting group to be considered in a synthetic process, it must fulfill specific requirements; the production of a selectively protected, stable substrate in quantitative yield which must then be capable selectively cleaving under mild conditions while not interfering with any other functional groups. [92] For example, some of the most common protecting groups for amines are *N*-*tert*-butoxycarbonyl (NBoc) (Fig. 3.2a), acetamide (NAc) (Fig. 3.2b), and acetoxy (OAc) (Fig. 3.2c). [93]

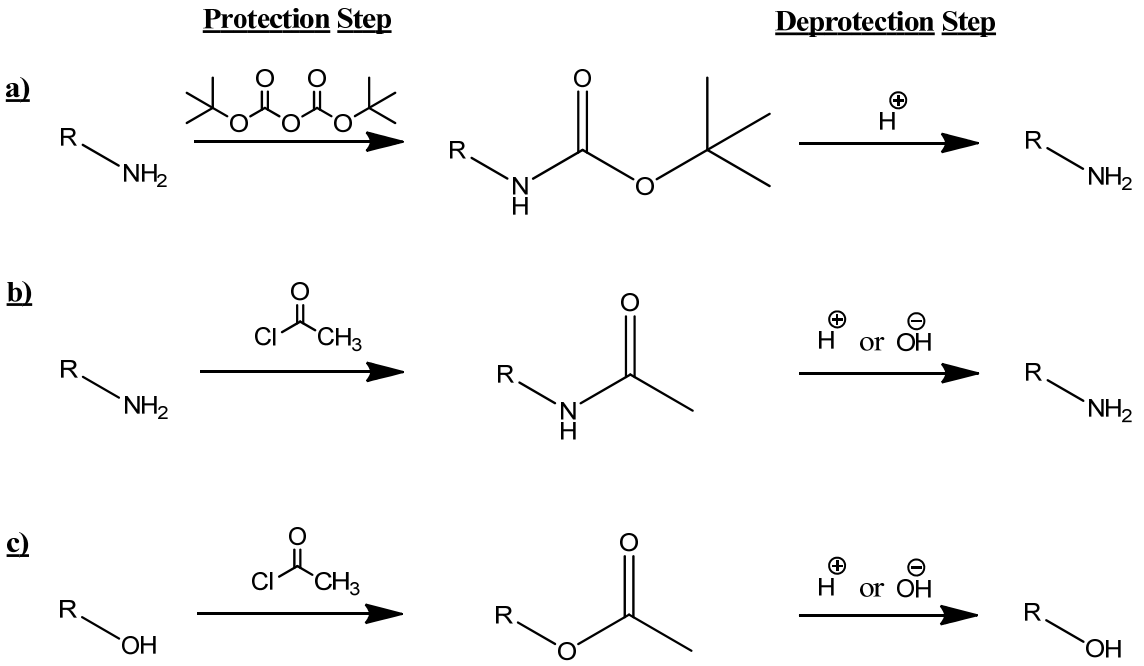


Figure 3.2: Protection and deprotection reactions: a) amines with an *N-tert*-butoxycarbonyl group (NBoc) b) amines with an acetamide group (NAc) c) alcohols with an acetoxy (OAc)

Among amine protecting groups, the NBoc group is perhaps one of the most widely used due to its stability towards a variety of reagents and reaction conditions. In addition, it can be readily removed by trifluoroacetic acid (TFA) in DCM [92]. However, to neutralize the acids or bases used in traditional deprotection reactions, an equimolar amount of subsequent base or acid is required for neutralization. This results in increasing the overall number of steps for the synthetic procedure, as well as the production of large amounts of salt and organic contaminated aqueous waste.

3.1.4 Deprotection Reactions using WET

Recently, employing WET for deprotection reactions as the solvent and catalyst has been studied in the elimination of environmentally hazardous solvents and acid catalysts. A few studies have also reported successful reactions using WET such as: mediation of acid/base catalyzed hydrolysis[94-97], Claisen-Schmidt condensation reactions[98], and acid catalyzed Friedel-Crafts alkylation reactions[99]. One of the most interesting applications of WET reported in literature is the deprotection of NBoc protected amines. [97, 100] In these studies, a variety of NBoc protected amines were deprotected using only water as the catalyst, reactant and solvent from a temperature range of 100-150°C. The reactions start with an NBoc derivative undissolved in water. Once the temperature is increased, the NBoc compound dissolves in the aqueous solvent and undergoes a deprotection reaction with the acidic water. Once the reaction comes back to room temperature, the deprotected amine product will separate from the aqueous phase. A schematic of this process is shown in Fig. 3.3.

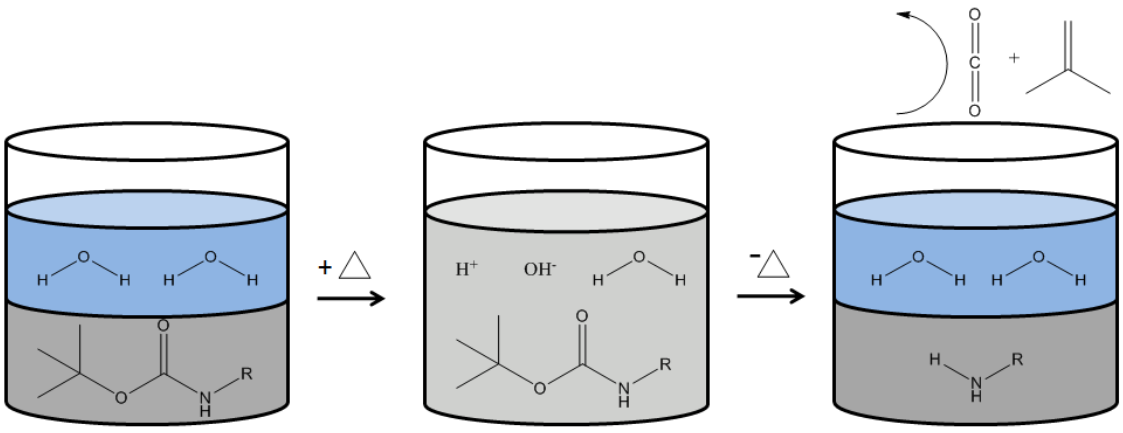


Figure 3.3: NBoc deprotection of amine compounds using WET

These examples were great proof-of-concept studies for the application of WET towards

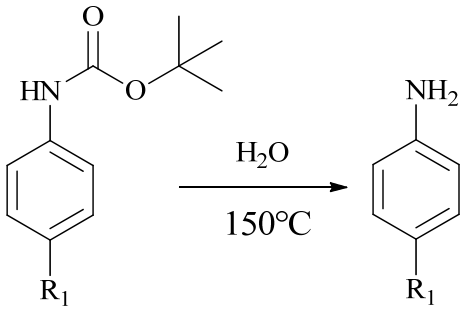
amine deprotection, but there were no further studies on the selectivity of the WET reaction or deprotection of other amine protected compounds. Therefore, in this thesis, we explored the selective removal of several protecting groups on model aryl compounds with multiple protected functionalities using WET.

3.2 Deprotection of Amines and Hydroxyl Protecting Groups using WET

3.2.1 Deprotection of Boc Groups from Aryl Amines using WET

Water at Elevated Temperatures (150°C), as a solvent and catalyst, was applied to the selective removal of the Boc-protected anilines with a variety of substituents as shown in Table 3.1.

Table 3.1: Deprotection of NBoc carbamates to anilines in water at 150°C



Entry	R_1	Time (min)	Yield (%)
1	H	16	85
2	OCH_3	30	87
3	Cl	84	100
4	NAc	10	98
5	NPiv	45	89

The *para* substituted anilines (H, OCH_3, Cl) investigated were found to have significant effects on the deprotection reaction rate. The effect of substituent is better seen in Fig. 3.4; showing the reaction yields as a function of time as monitored by HPLC.

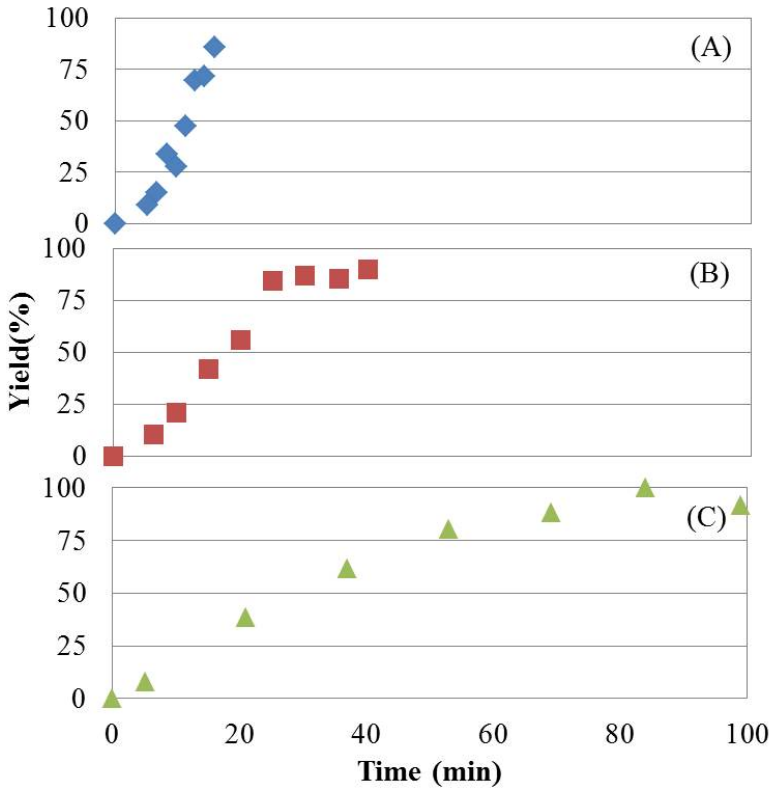


Figure 3.4: Removal of NBoc group from protected anilines as a function of time: (A) yield of aniline (Table 3.1, Entry 1), (B) yield of *p*-methoxyaniline (Table 3.1, Entry 2), (C) yield of *p*-chloroaniline (Table 3.1, Entry 3)

From these graphs, the observed trend is as follows: when R_1 = H > OCH_3 > Cl the reaction time to completion was 16, 30 and 84 minutes, respectively. This contradicts our initial theory which takes the electronic effects of the R_1 substituent into consideration. If these electronic effects were dominant, the electron withdrawing groups would facilitate a faster deprotection reaction due to the increased electrophilicity of the Boc group in the following order (OCH_3 > Cl > H). This observation is attributed to the dissolution rate of the starting materials: the solubility of the staring materials in water was greatest when R_1 = H and lowest when R_1 = Cl. The rate at which the starting material can dissolve affects

the speed of deprotection, because the reaction can only take place in solution. The competitive removal of *N*-Boc versus *N*-Ac protecting groups from the para substituted anilines was also investigated (Table 3.1, entry 4 and 5). The rate of deprotection of the Boc groups from entries 4 and 5 as a function of time is represented in Fig. 3.5.

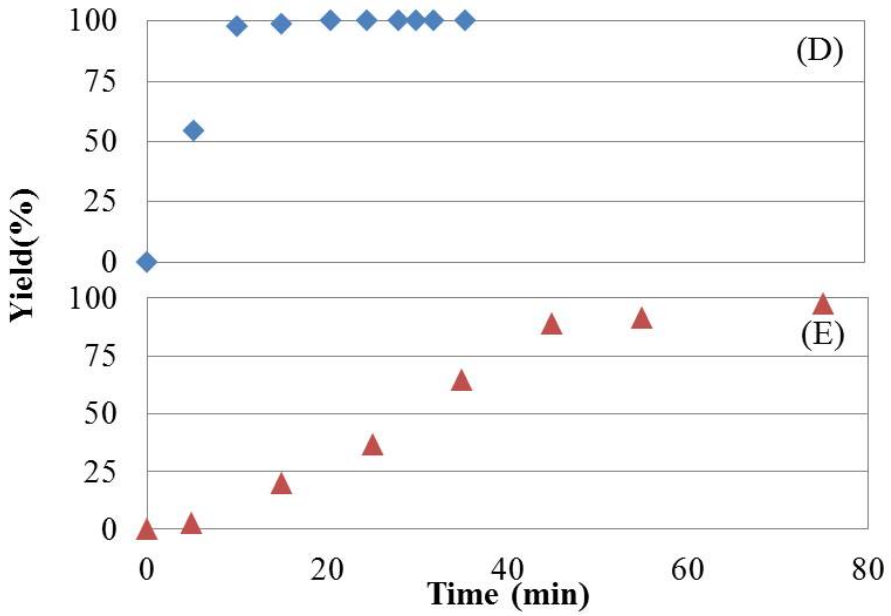


Figure 3.5: Removal of NBoc group of different protected anilines containing a secondary amine-protecting group as a function of time: (D) Reaction of *N*-(4-aminophenyl)acetamide (Entry 4), (E) Reaction of *N*-(4-aminophenyl)pivalamide (Entry 5)

In these cases, the NBoc groups were selectively cleaved to the corresponding amines in high yields using WET (150°C), while the amide substituents remained intact. The time to completion was 35 minutes longer for the amine with the Pivaloyl (Piv) group. As with Table 3.1- entries 1, 2 and 3, the dissolution rate of the substrate has a significant effect on the resulting rate of deprotection. The Piv moiety is less soluble in water than the

acetyl group (Ac), making the dissolution rate is slower. These observations further demonstrate that the solubility properties of the starting material are the dominant factor in the time to completion.

3.2.2 Appearance of 1,3 Diphenylurea and Reaction Mechanism Possiblilties

During the course of the above experiments, an unknown additional peak was observed on the HPLC chromatogram of the deprotected anilines. Figure 3.6 shows the HPLC chromatograms for the removal of the Boc protecting group from N-Boc aniline using WET (150°C) as a function of time.

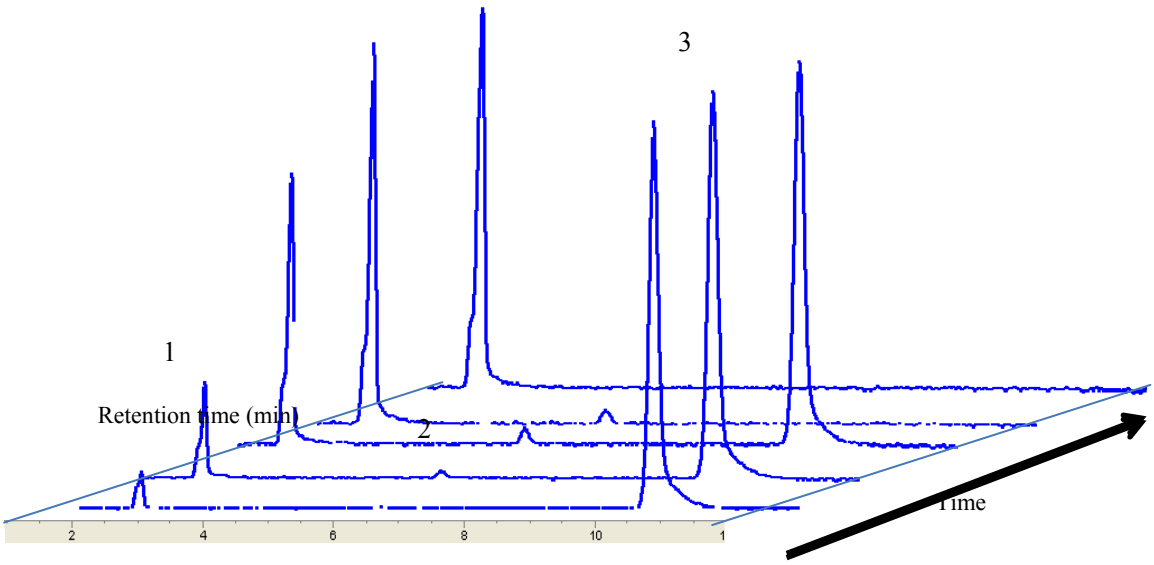


Figure 3.6: HPLC chromatograms for the removal of the Boc group from N-Boc-aniline (peak 3) to aniline (peak 1) showing the appearance of 1,3-diphenylurea (peak 2)

Using Liquid Chromatography Mass Spectrometry (LC-MS), the molecular weight

associated with the unknown peak 2 (Fig. 3.6) was determined to be 212 g/mol, consistent with the structure of 1,3-diphenylurea. It should be noted that the 1,3-diphenylurea is not present at the beginning of the WET (150°C) deprotection reaction, but evolves at sometime during the reaction. By completion, the 1,3-diphenylurea is not detected in the products. With this new development, we hypothesized that the urea could be acting as an intermediate in the WET (150°C) deprotection reaction. Fig. 3.7 demonstrates a possible reaction pathway from *N*-Boc-aniline to aniline through the urea intermediate.

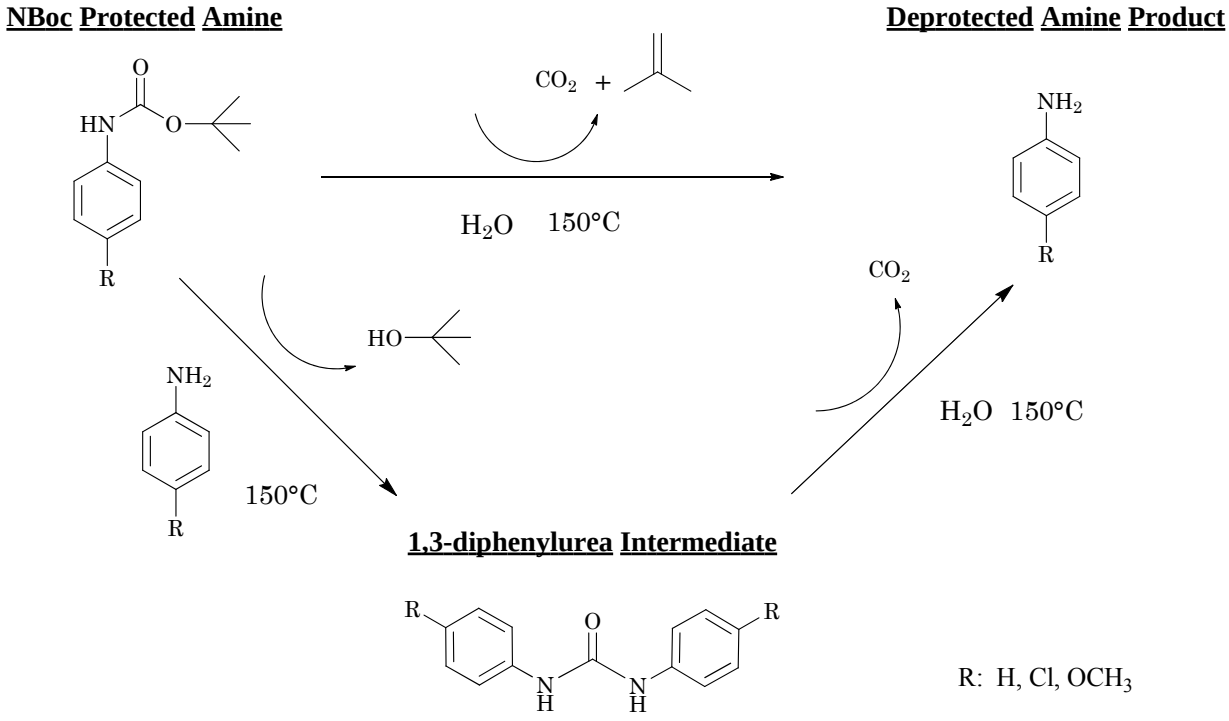


Figure 3.7: Possible pathway to aniline products from the WET reaction

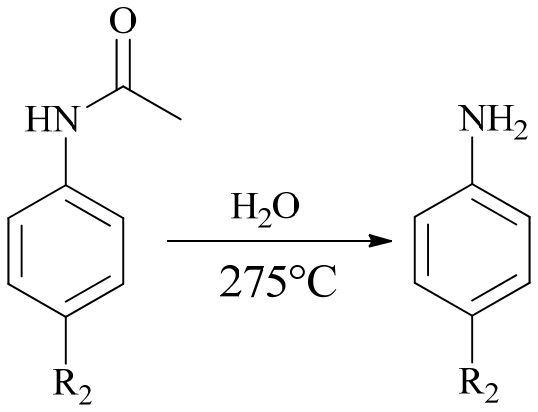
In this proposed pathway, the deprotected amine product can act as a nucleophile and react with the protected NBoc starting material to from the 1,3-diphenylurea

intermediate. The resulting urea intermediate will react with water to produce the final deprotected amine product.

3.2.3 Deprotection of Acetyl Groups from Aryl Amines using WET

In Table 3.1, entry 4, the NAc group (an acetamide) remained intact at 150°C for 10 minutes while the NBoc group was deprotected. Demonstrating the tunable properties of the WET system, the deprotection of acetamides to their corresponding amines using WET at 275°C was investigated (Table 3.2). We monitored the yield of the amines as a function of time from the conversion of the acetamides.

Table 3.2: Deprotection of acetamides to amines at 275°C



Entry	R_2	Time (min)	Yield (%)
1	H	250	35
2[a]	H	250	97
3	OCH_3	400	46
4[a]	OCH_3	400	90

[a] Reaction conducted with deoxygenated water under a nitrogen atmosphere.

Two of the reactions proceeded under the presence of oxygen (Table 3.2, Entries 1 and 3). The yields were very low (35% and 46%, respectively) compared to the previous NBoc reactions. Using LC-MS analysis, it was identified that phenazine (m/z= 180) was a major byproduct (Fig. 3.8).

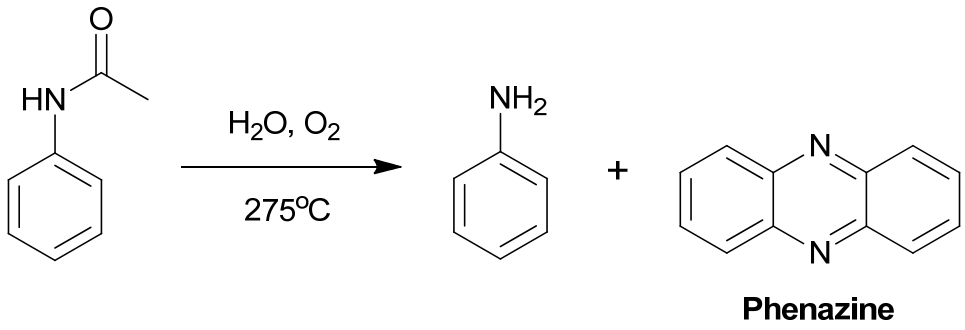


Figure 3.8: Reaction of N-phenylacetamide in the presence of oxygen

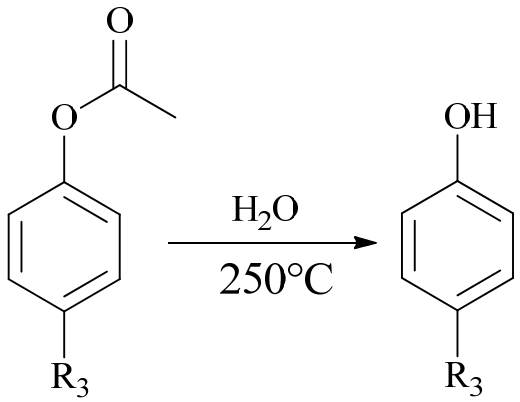
Phenazine would only form in oxidative conditions (O_2 atmosphere), so the reactions were repeated with under a N_2 atmosphere (Table 3.2 Entries 2 and 4). With this modification, the yield of the deprotected amine in the absence of oxygen is very high with only traces of phenazine being detected. Another interesting observation from Table

3.2 is the time to completion (400 minutes) of the para substituted examples compared to the unsubstituted examples (250 minutes). This outcome can again be explained by solubility effect of the starting compounds in water (R_2 = H was more soluble).

3.2.4 Deprotection of Acetyl Groups from Phenols using WET

After exploring amine deprotections at 150°C and 275°C, the WET conditions applied to acetates (protecting group for hydroxyls) at 250°C (Table 3.3).

Table 3.3: Deprotection of acetates to alcohols at 250°C



Entry	R_3	Time (min)	Yield (%)
1	H	20	92
2	NAc	30	99

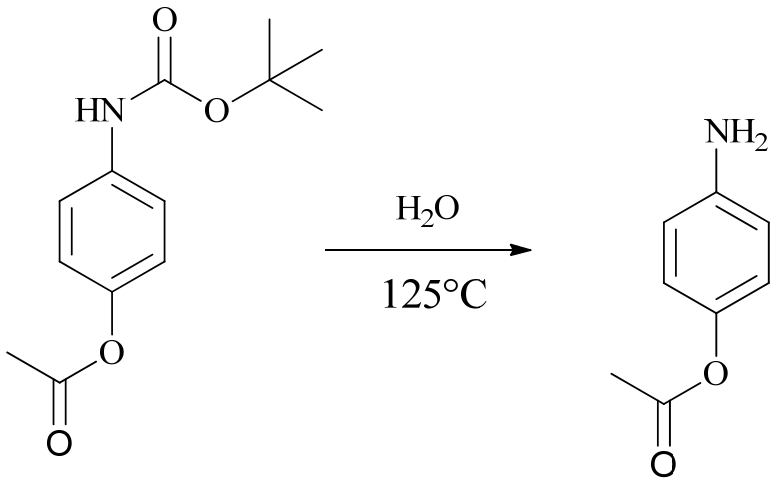
These reactions proceeded very rapidly, essentially complete in 30 minutes or less with both acetate compound achieving yields above 90%. In the case of the 4-

acetamidophenyl acetate (Table 3.3, Entry 2), the complete selective deprotection of the acetate group was observed under these conditions leaving the amide group intact. This result exploits the temperature dependent physical properties that WET can achieve.

3.2.5 Selective Deprotection of NBoc Groups over OAc Groups from Aryl Amines using WET

The deprotection of NBoc to an amine was demonstrated at 150°C. At 250°C, acetates could easily be deprotected to a hydroxyl group, but this reaction can take place at temperatures close to 150°C, albeit at a slower rate. Therefore, the selectivity of the deprotection of the NBoc over OAc was tested with 4-((tert-butoxycarbonyl)amino)phenyl acetate at 125°C (Table 3.4).

Table 3.4: Selective deprotection of NBoc over OAc group at 125°C.



Temperature	Time (min)	Yield (%)
125°C	90	78

The NBoc group was selectively deprotected while the OAc group remained unreacted in 78% yield. Once again it is shown that the temperature can be tuned to achieve selective deprotection. In this example, it is shown that protected hydroxyl groups (OAc) can stay protected while the NBoc amine can be converted to an amine.

3.3 Conclusions

In this chapter, a selective and, more importantly, tunable mechanism to deprotect aryl carbamates, amides, and acetates to anilines and phenols was demonstrated. The WET deprotection mechanism exploits the temperature dependent properties of water by varying the temperature of the reactions. For the deprotection of NBoc, NAc, and OAc the reaction temperature was 125°C, 250°C, and 275°C, respectively. An important finding of this work was the atmospheric dependence of the deprotection of NAc. These reactions must be done in the absence of oxygen to avoid oxidation to the major phenazine byproduct. Overall, the deprotection reaction rates across all substrates were most affected by dissolution rates which depended on the solubility of the starting material.

3.4 Recommendations

The deprotection reactions with WET were shown with Boc and Ac groups, but there are other protecting groups that could potentially be used. Fluorenylmethyloxycarbonyl (Fmoc) is another popular protecting group for amines and is sensitive to basic conditions. Acetals are protecting groups for carbonyls and the deprotection can take place in acidic mediums. [93]

3.5 Experimental

3.5.1 Synthesis Procedures

Representative Procedure for the Water at Elevated Temperature Study

The reactions were performed in closed 3 mL titanium batch reactors. These reactors were designed and produced in-house and were sealed with titanium NPT plugs. Titanium was used as the material of construction due to the very low level of transition metals and corrosion resistance of the metal. 316 Stainless Steel reactors have been found to catalyze unwanted side reactions during investigations conducted within our research group. The reactors were loaded to have an approximate concentration of 0.033M with a volume of water of 1.5 mL. The titanium reactors were then placed in a thermostated aluminum heating block. The temperature of the heating block varied by ±1°C and was maintained using four cartridges heaters (Omega Technologies Co.) and a temperature controller (Omega Model CN76000). An over-temperature probe (I^2R Model OTP-1500) was also employed as safety precaution to prevent the block from overheating in the case of a temperature controller failure. The heating block was

preheated to desire temperatures ranging from 150-275°C and the pressures in the individual reactors was generated solely by the expansion of the liquid medium (approximately 70 to 580 psi). The reactors reached the reaction temperatures in less than 5 minutes and were withdrawn at various reaction times and quenched in a room temperature water bath. Upon completion, the reactor contents were diluted in acetonitrile in a single phase and separated and quantified using HPLC (HP 1100 with a UV detector using a Phenomenex Luna 5µm C18(2) reverse phase column) and LCMS (Waters Alliance 2965 Separations Module with a Waters 2998 PDA and a Waters 3100 SQD MS (ESI positive) using a Phenomenex Luna C18(2) column (3 µm, 4.6 x 75mm)).

Synthesis of *tert*-Butyl(4-methoxyphenyl)carbamate

p-Methoxyaniline (0.82 g, 6.7 mmol) and di-*tert*-butyl dicarbonate (Boc_2O, 2.2 g, 10 mmol) were stirred in 25 mL absolute ethanol overnight at room temperature. The solvent was removed by rotary evaporation. The resulting solid was dissolved in diethyl ether (Et_2O, 30 mL) and washed three times with water (H_2O, 30 mL). The organic layer was dried over magnesium sulfate ($MgSO_4$), filtered, and the solvent was removed on the rotovap.

Synthesis of tert-Butyl(4-chlorophenyl)carbamate

p-Chloroaniline (0.85 g, 6.7 mmol) and di-tert-butyl dicarbonate (Boc_2O, 2.2 g, 10 mmol) were stirred in 25 mL absolute ethanol overnight at room temperature. The solvent was removed by rotary evaporation. The resulting solid was dissolved in diethyl ether (Et_2O, 30 mL) and washed three times with water (H_2O, 30 mL). The organic layer was dried

over magnesium sulfate ($MgSO_4$), filtered, and the solvent was removed on the rotovap.

Synthesis of *tert*-butyl (4-acetamidophenyl)carbamate

To 2 g (0.00960 mol) of NBoc-p-phenylenediamine was added 200 mL anhydrous DCM under nitrogen with stirring in an ice-water bath. 1.0 mL (0.0124 mol) of anhydrous pyridine was added dropwise to the cold solution. The reaction mixture was stirred for 10 min and 1 mL (0.0106 mol) of acetic anhydride was added dropwise. After 10 min of stirring, the ice-water bath was removed and the reaction proceeded at room temperature for 4 hrs. The reaction mixture was neutralized with saturated sodium carbonate under vigorous stirring. Additional water and DCM were added and the organic layer separated, dried, and evaporated under reduced pressure. The product was recrystallized in toluene. The white solid was filtered, washed with toluene, and dried in a vacuum oven overnight yielding 0.903 g of product (82%).

Synthesis of tert-butyl (4-pivalamidophenyl)carbamate

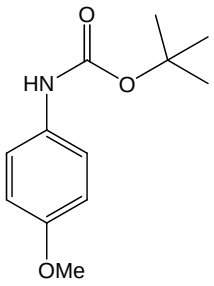
To 0.8 g (0.00384 mol) of *N*-Boc-*p*-phenylenediamine was added 65 mL anhydrous DCM under nitrogen with stirring in an ice-bath. 0.350mL (0.0043 mol) of anhydrous pyridine was added dropwise to the cold solution. The reaction mixture was stirred for 10 min. and 0.512 mL (0.00416 mol) of pivaloyl chloride was added dropwise. After 10 min. of stirring, the ice-water bath was removed and the reaction proceeded at room temperature for 4 hrs. The reaction mixture was neutralized with saturated sodium carbonate under vigorous stirring. Additional water and DCM were added and the organic layer separated, dried, and evaporated under reduced pressure. The product was

recrystallized from toluene. The white solid was filtered, washed with toluene, and dried in a vacuum oven overnight yielding 0.903 g of product (80%).

Synthesis of 4-((*tert*-Butoxycarbonyl)amino)phenyl acetate

A 25 mL round bottom flask was charged with 0.75 g (0.00496 mol) of 4-aminophenyl acetate and 1.37 g (0.00595 mol) of melted (about 40°C) of di-*tert*-butyl dicarbonate. 0.12 g (5% mol) of ground $Bi(NO_3)_3 \cdot 5H_2O$ was added to the neat mixture. The mixture was stirred at 40°C for 10 minutes. Water was added to the mixture and the organics were extracted with ethyl acetate. The organic layer was dried with $MgSO_4$, filtered and the solvent removed by rotary evaporation. The crude was purified with on a silica column with hexane:ethyl acetate (80:20, 50:50). 0.76 g (61%) of product (white solid) isolated.

3.5.2 Spectral Data



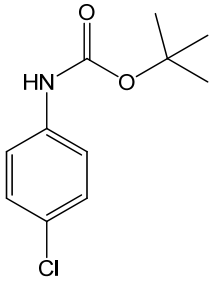
***tert*-Butyl(4-methoxyphenyl)carbamate**

Color and State: White Solid

^{1}H NMR (400 MHz, DMSO-d6) δ 9.11 (s, 1H), 7.33 (d, 2H), 6.81 (d, 2H), 3.68 (s, 3H), 1.44 (s, 9H).

^{13}C NMR (400 MHz, DMSO-d6) δ 153.96, 152.44, 132.09, 119.16, 113.30, 78.14, 54.52, 27.67.

M.P. 95-96°C



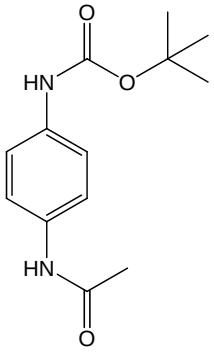
***tert*-Butyl(4-chlorophenyl)carbamate**

Color and State: White Solid

^{1}H NMR (400 MHz, DMSO-d6) δ 9.49 (s, 1H), 7.46 (d, 2H), 7.27 (d, 2H), 1.45 (s, 9H).

^{13}C NMR (400 MHz, DMSO-d6) δ 152.18, 138.04, 128.00, 125.09, 119.03, 78.84, 27.58.

M.P. 102 – 103°C



***tert*-butyl (4-acetamidophenyl)carbamate**

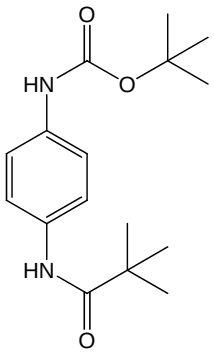
Color and State: White Solid

^{1}H NMR (400 MHz, DMSO-d6) δ 1.46 (s 9H), 2.00 (s 3H), 7.34 (d 2H), 7.43 (d 2H), 9.20 (s 1H), 9.78 (s 1H).

^{13}C NMR (400 MHz, DMSO-d6) δ 23.84, 28.14, 78.81, 118.50, 119.52, 133.89, 134.79, 152.85, 167.86

MS (ESI+): 151.1 m/z

EA Theoretical: C 62.38%, H 7.25%, N 11.79%. Found: C 62.35%, H 7.36%, N 11.07%.



***tert*-butyl (4-pivalamidophenyl)carbamate**

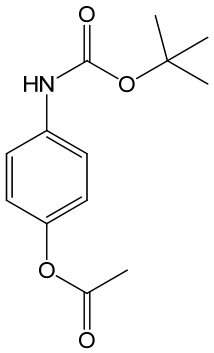
Color and State: White Solid

^{1}H NMR (400 MHz, DMSO-d6) δ 1.21 (s 9H), 1.47 (s 9H), 7.36 (d 2H), 7.49 (d 2H), 9.07 (s 1H), 9.22 (s 1H).

^{13}C NMR (400 MHz, DMSO-d6) δ 27.29, 28.17, 38.96, 78.79, 118.10, 120.90, 133.78, 134.96, 152.82, 176.09

MS (ESI+): 193.3 m/z.

EA Theoretical**:** C 65.73%, H 8.27%, N 9.58%. Found: C 66.00%, H: 8.12%, N: 9.48%



4-((*tert*-butoxycarbonyl)amino)phenyl acetate

^{1}H NMR (400 MHz, CDCl3) δ 1.49 (s, 9h), 2.25 (s, 3h), 6.76 (broad, 1h), 6.99-6.95 (dt, 2h), 7.34-7.32 (d, 2h).

^{13}C NMR (400 MHz, CDCl3) δ 20.98, 28.24, 80.48, 119.34, 121.81, 136.03, 145.84, 152.72, 169.66.

EA Theoretical: C: 62.14%, H: 6.82%, N: 5.57%. Found: C: 61.61%, H: 7.14%, N: 4.95%.

MS (ES+): 252m/z.

APPENDIX A

A STUDY OF OXAZOLINE PROTECTED REAGENTS FOR THE KNOEVENAGEL CONDENSATION

A.1 Hemetsberger Indolization Background

Indoles are important compounds and have previously been introduced in Chapter 1 section 1.1.3. There are a variety of ways of producing the indole moeity, but the Fischer Indolization is the most popular in industrial settings (Fig. A.1).

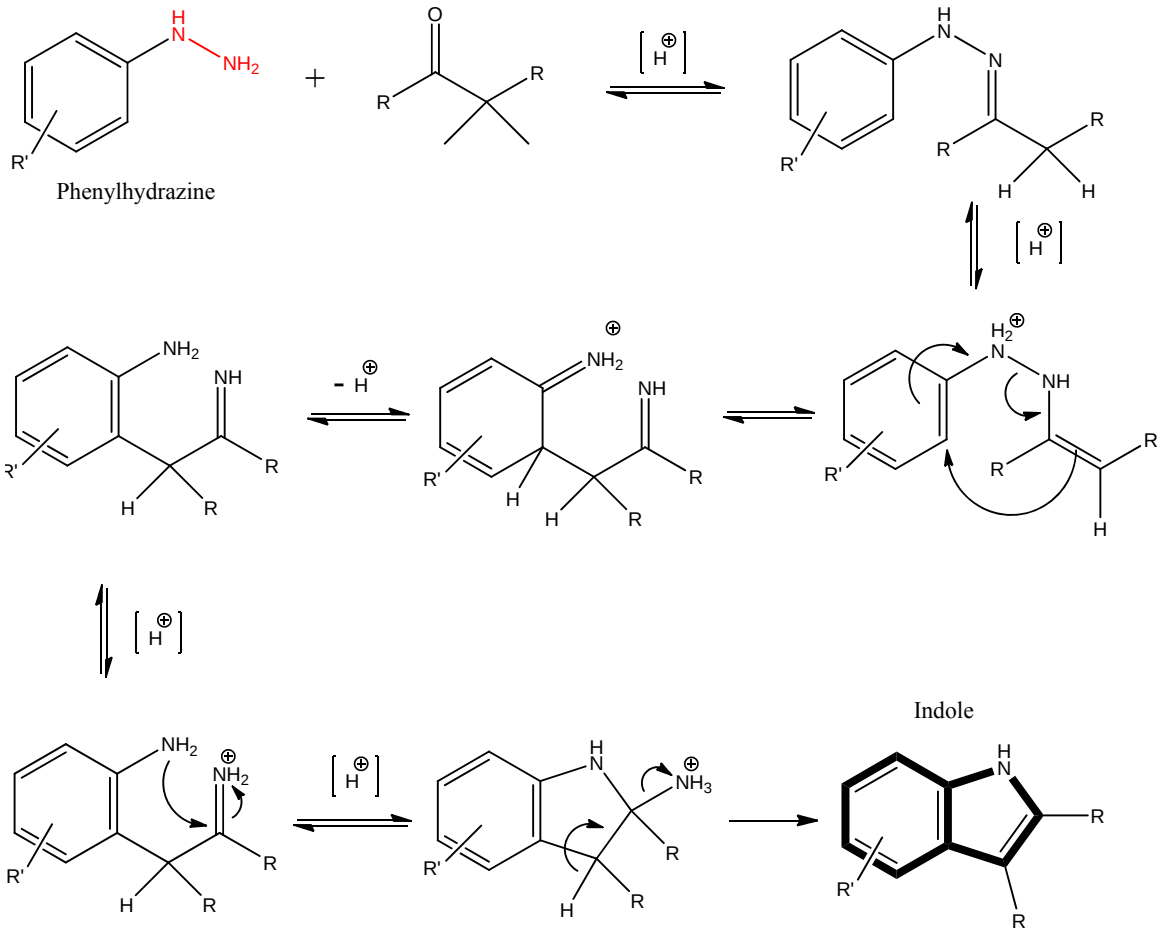


Figure A.1: Fischer Indolization Process starting with Phenylhydrazine

Another popular route to indoles is the Hemetsberger indolization. [101-106] Of these two methods, the Hemetsberger indolization seems to be the most facile, since it only uses heat to cyclize an α-azido-β-arylacrylates starting material. The Hemetsberger indolization has also been shown to be successful in a continuous flow process, which may be more suitable to industrial scale synthesis. [107] The total synthesis to form an indole by the Hemetsberger indolization involves three steps: the synthesis of an alkyl azidoacetate (1), a base-promoted Knoevenagel condensation between an azidoacetate and an aryl aldehyde to form an α-azido-β-arylacrylate (2), and finally the thermolysis of the α-azido-β-arylacrylate to form an indole via an intramolecular cyclization (3) (Fig. A.2).

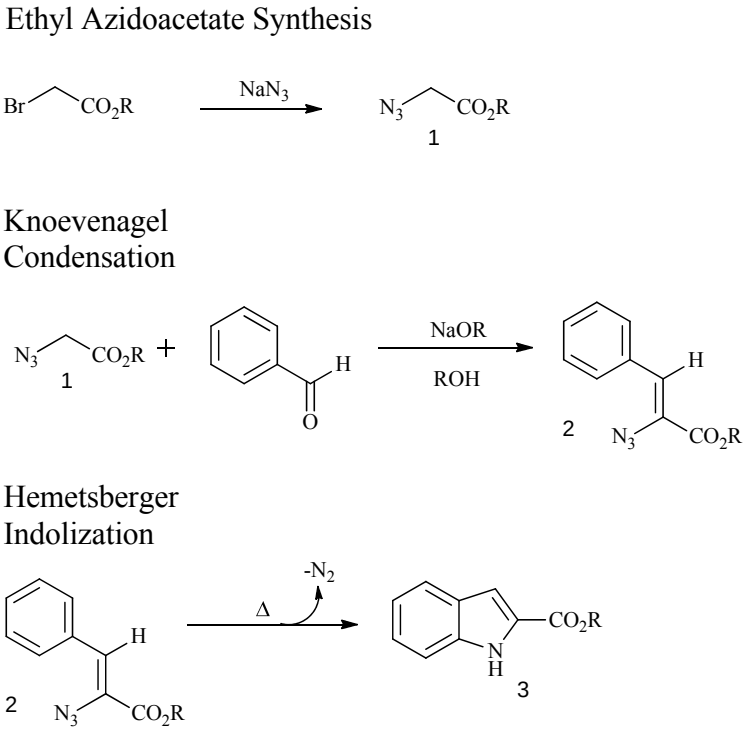


Figure A.2: Total synthesis of indoles: the ethyl azidoacete synthesis, the Knoevenagel condensation, and the Hemetsberger indolization

The biggest limitation to the widespread acceptance of the Hemetsberger indolization in industrial processes is the low yields associated with the synthesis of the α-azido-β-arylacrylate precursors in the Knoevenagel condensation step. The yields of α-azido-β-arylacrylates have been reported to range from low (10%) to moderate (64%). [103, 107-110] There are two major reasons for these low yields: the instability of azidoacetates in the presence of base and the hydroxide promoted hydrolysis of the ester group in the α-azido-β-arylacrylate. Esters can be protected as an oxazoline in reaction where ester groups can be sensitive to reaction conditions. [111] The oxazoline can be deprotected back to the ester in acidic conditions (Fig A.3).

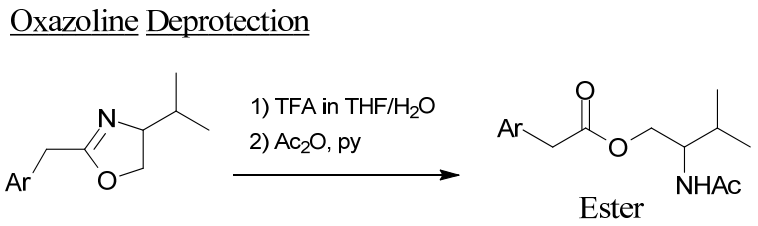


Figure A.3: Deprotection of an oxazoline to an ester functional group. [112]

A.2 Hemetsberger Indole Synthesis with Oxazoline

To prevent the hydrolysis of the ester group during the Knoevenagel condensation, it may be possible for the reaction to have increased yields with an oxazoline protecting group (Fig. A.4).

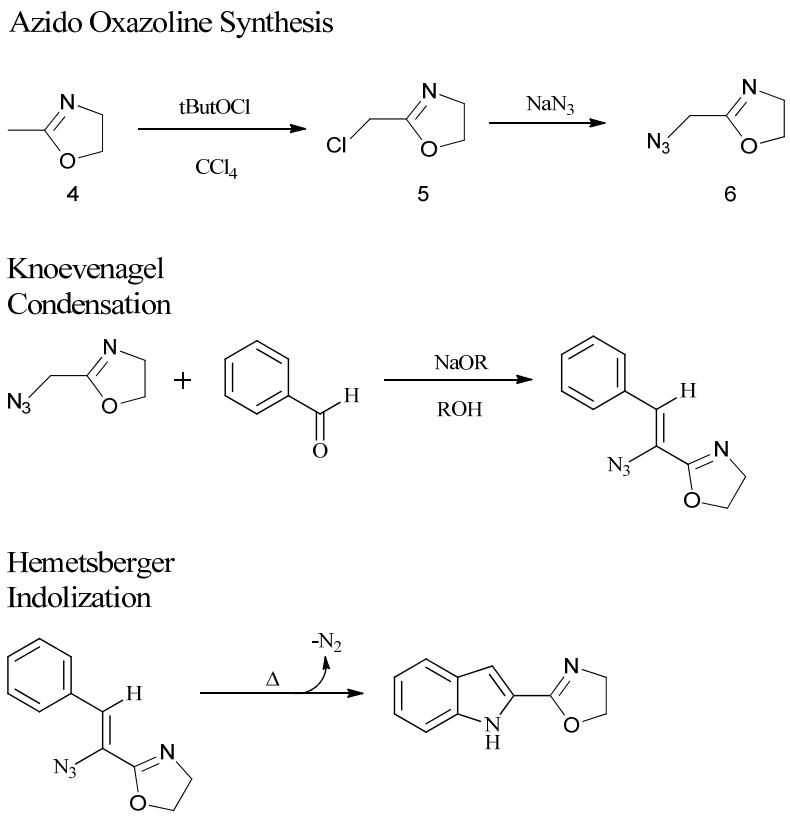


Figure A.4: Proposed total synthesis of indoles: the azido oxazoline synthesis, the Knoevenagel condensation, and the Hemetsberger indolization

The oxazoline moiety is base stable, so the hydrolysis should not occur. However, 2-azidomethyl-2-oxazoline (6) has not been synthesized in literature, so it may be difficult to prepare. The first step in the synthesis of the 2-azidomethyl-2-oxazoline (6) was accomplished from a radical reaction of 2-methyl-2-oxazoline (4) with t-butyl hypochlorite in carbon tetrachloride to produce 2-chloromethyl-2-oxazoline (5). The product was isolated as an oil in 77% yield after short-path vacuum distillation. Next, (5) was reacted with sodium azide in ethanol at 78°C for 18hrs, but the resulting reaction mixture was a purple crude sludge (Fig. A.5).

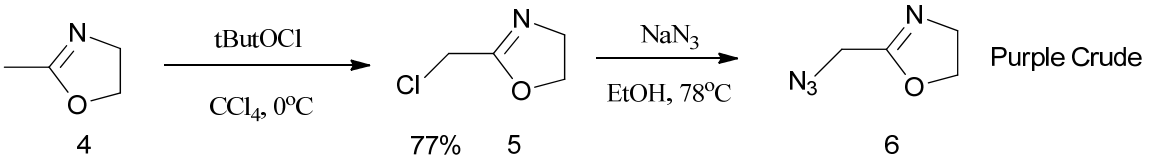
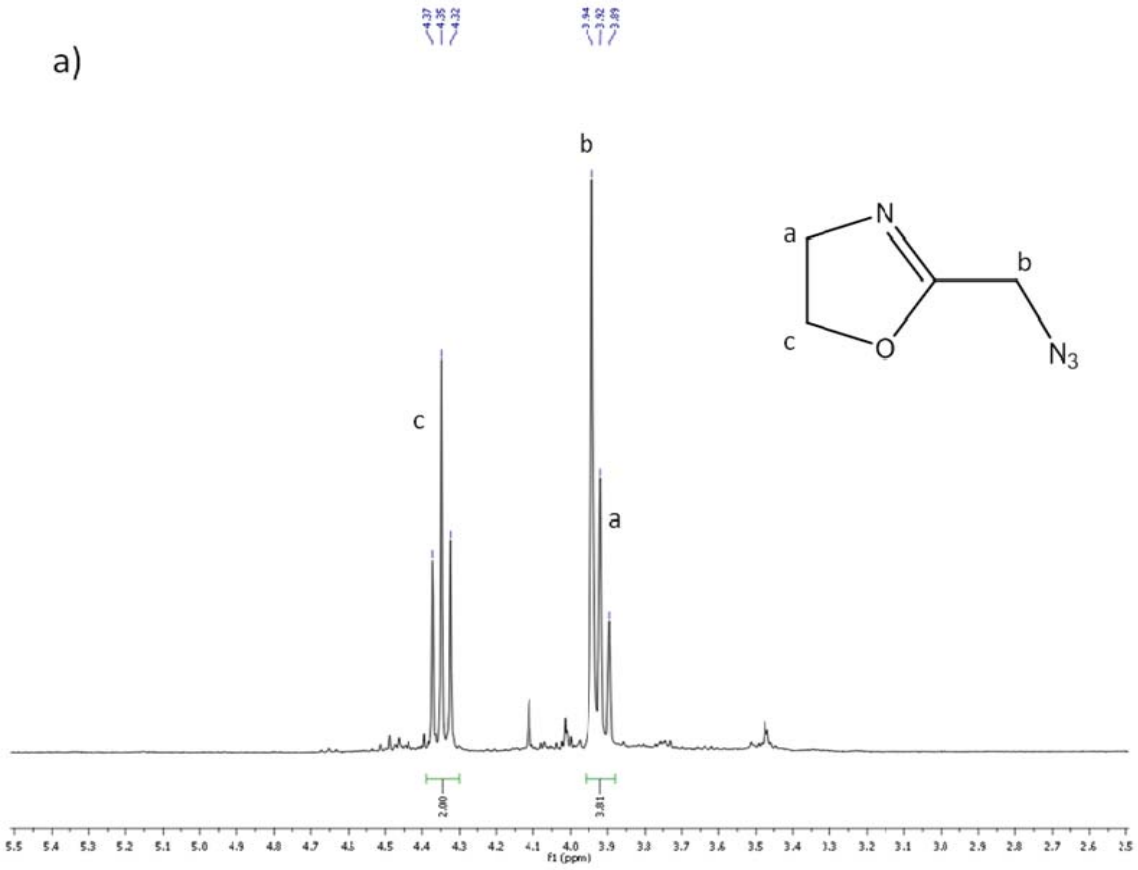


Figure A.5: Synthesis of 2-azidomethyl-2-oxazoline

The purple crude was could not be evaluated with further purification. Using a Kugelrohr distillation at 50°C for 1 hr, 6 was isolated in about 3% yield as a clear liquid, but after 30 minutes at room temperature the product evolved a light red complexion. ^{1}H NMR spectra before and after the 30 minute period revealed that 2-azidomethyl-2-oxazoline undergoes decomposition (Fig. A.6).



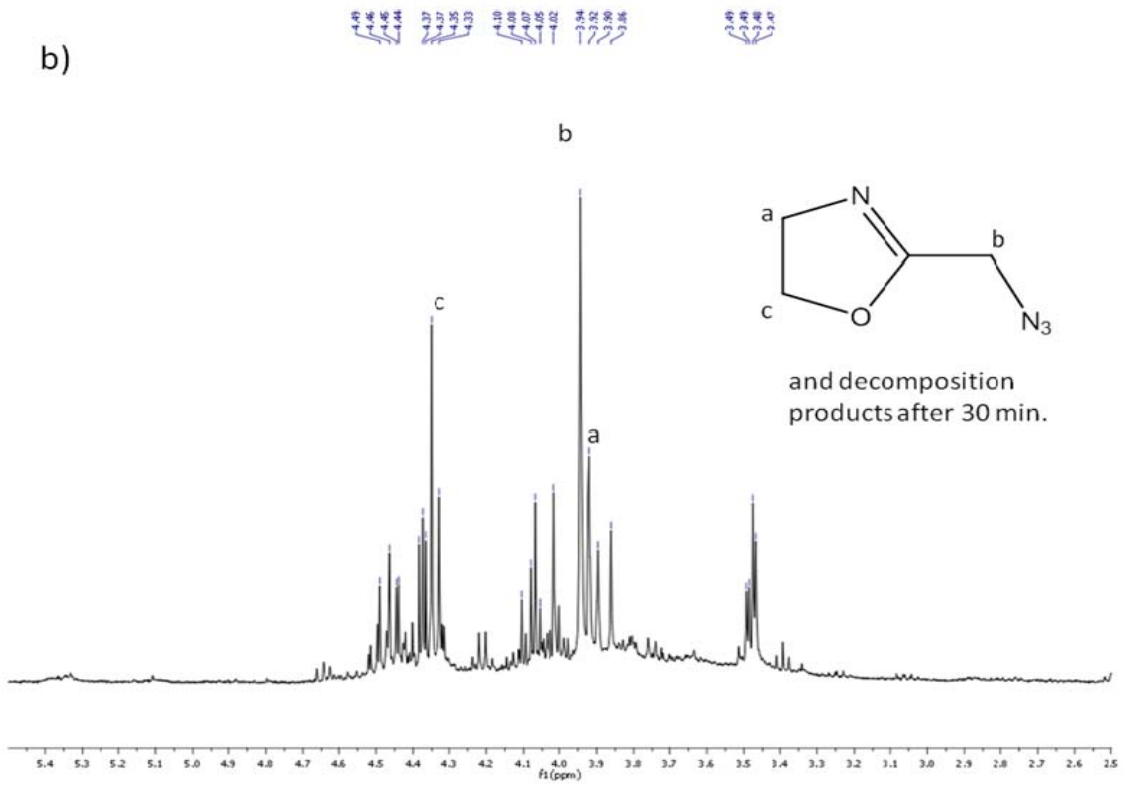


Figure A.6: a) ^{1}H NMR of the azido oxazoline after purification from distillation b) ^{1}H NMR of the azido oxazoline 30 minutes after isolation

The spectra clearly show that 2-azidomethyl-2-oxazoline is not stable and will not be a good candidate for a protecting group for the Knoevenagel condensation. It may be possible that compound 6 could be undergoing a ring opening at the carbon alpha to the nitrogen due to nucleophilic attack. Therefore, a study with a 4,4-dimethyl substituted oxazoline was performed to sterically hinder a nucleophilic attack. From 2,4,4-trimethyl-2-oxazoline, the same procedure was as in figure A.4 was followed to synthesize 2-(azidomethyl)-4,4-dimethyl-4,5-dihydrooxazole (9) (Figure A.7).

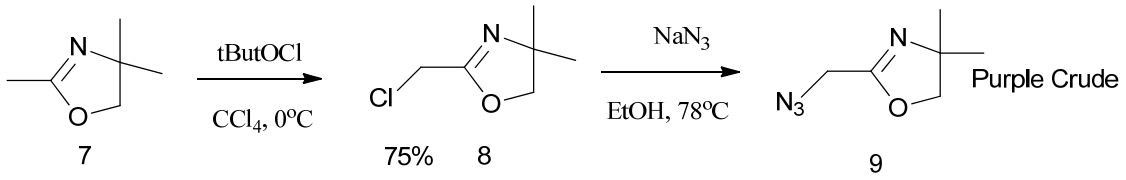


Figure A.7: Total synthesis of 2,4,4-trimethyl-2-oxazoline

Unfortunately, the synthesis of 9 followed the same short coming of the previous synthesis and could not be isolated (and the same purple color evolved). These studies concluded that both azidomethyl oxazolines (6 and 9) are not stable at ambient conditions and are not suitable for further steps in the Knoevenagel and Hemetsberger reactions. In a parallel study by Dr. William Heaner, the Knoevenagel reaction was successful with a benzoxazole protecting group (Fig. A.8). The reaction yielded 25% of the Knoevenagel product, 2-(a-azido-b-phenyl)benzoxazole. [113]

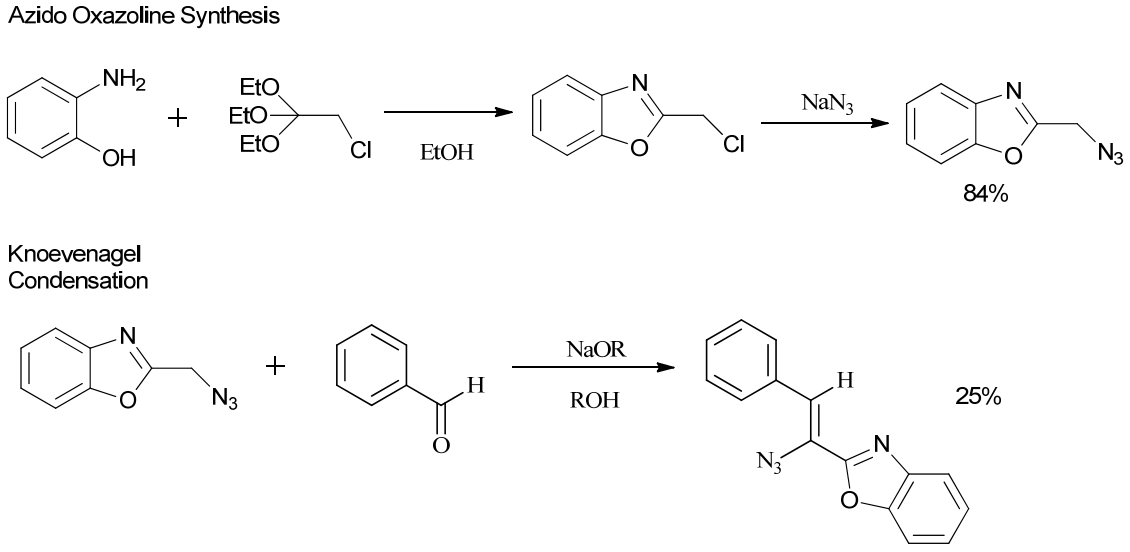


Figure A.8: Knoevenagel condensation with a benzoxazole protecting group

The paper discovered that 2-(α-azido-β-phenyl)benzoxazole undergoes a competitive degradation in the presence of base to form products of unknown structures. Therefore, both oxazolines and oxazoles were moieties not suitable for the Knoevenagel condensation. The instability of the azido oxazoline could be for several different reasons. Azides are known to undergo thermal decomposition to a reactive nitrene. [114] Once a nitrene is formed, this species very electrophilic and known to undergo reactions such as C-H insertion (Figure A.9a). [115-117] Another explanation could be that the azide promotes tautomerization of the oxazoline. The tautomers may be more reactive and undergo undesirable side reactions (Figure A.9b). Also, oxazolines are known to react through ring opening reaction. [118] If the oxazoline nitrogen interacts with an electrophile, then the oxazoline ring can open to a new species (Figure A.9c).

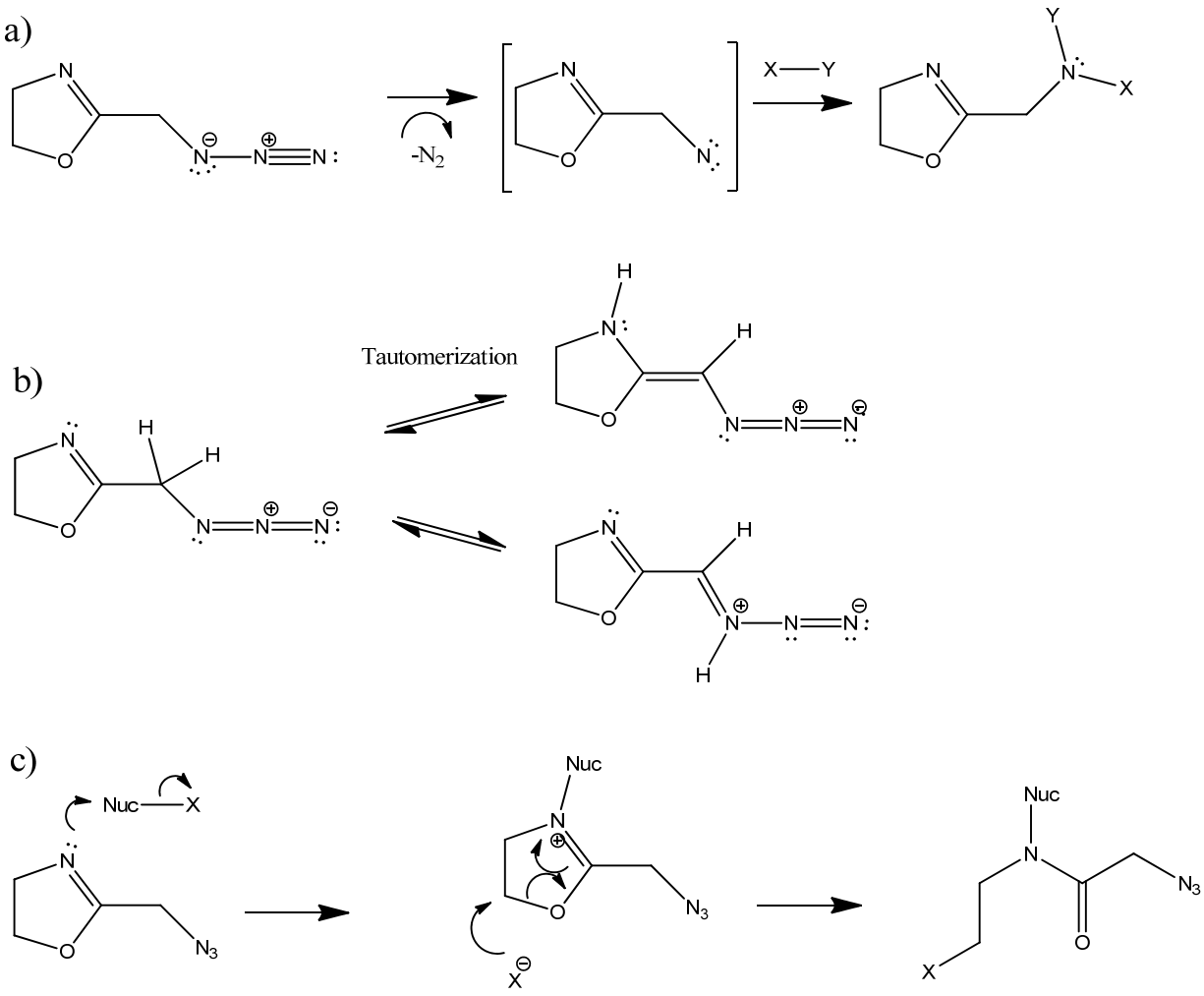


Figure A.9: a) Decomposition example of the azide to nitrene reaction b) Decomposition example of tautomerization of the azido oxazoline c) Decomposition via a ring opening reaction of the azido oxazoline

A.3 Conclusions

In efforts to increase the yields of the Knoevenagel reaction, both oxazolines and oxazoles protecting groups were employed to prevent hydrolysis of the ester group. The synthesis of both 2-azidomethyl-2-oxazoline 2-(azidomethyl)-4,4-dimethyl-4,5-

dihydrooxazole were unsuccessful. Using a benzoxazole protecting group, the Knoevenagel reaction to 2-(α -azido-β -phenyl)benzoxazole was successful, but the yield was very low (25%). It was concluded that oxazolines and oxazoles were not suitable for the Knoevenagel condensation.

A.4 Experimental

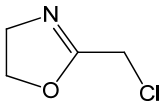
Representative synthesis of 2-(chloromethyl)-4,5-dihydrooxazoles (5,8)

To a 150 mL round bottom flask, 45 mL of CCl_4 solvent was added under argon. While stirring 4.5 mL (4.5 g, 0.052 mol) of 2-methyl-2-oxazoline (4) was added to the flask. In the dark, 5.5 mL (5.28 g, 0.049 mol) of freshly prepared tBuOCl was added while stirring. The flask was wrapped in aluminum foil and the reaction was stirred for 19 hours. To quench the hypochlorite, 2 g sodium bisulfate in 20 mL of distilled water (10% w/v solution) was added to reaction mixture and the organic layer was separated in a separatory funnel. The organic layer was dried with magnesium sulfate, filtered, and the solvent was removed under rotary evaporation to obtain a colorless, crude oil. 4.33 g (77%) of (5) was isolated from vacuum kugelrohr distillation at 50°C.

Synthesis of 2-(azidomethyl)-4,5-dihydrooxazoles (6)

In a 100 mL, 3-neck round bottom flask fitted with a condenser, 1.6 g (0.032 mol) of NaN3 was added. The vessel was sparged with argon and 40 mL of anhydrous ethanol was added. To the heterogeneous mixture, 1 g (0.008 mol) of chloromethyl-2-oxazoline was added. The reaction was heated to 78 °C and reacted for 19 hours. After 19 hrs.,

ethanol was removed under vacuum to produce a dark purple crude. 31 mg of product (3%) was isolated after vacuum kugelrohr distillation at 60°C.



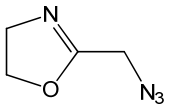
2-(chloromethyl)-4,5-dihydrooxazole (5)

Color and State: Colorless Oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79-3.74 (t, 2H), 3.98 (s, 2H), 4.24-4.19 (t, 2H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 163.45, 68.56, 54.65, 36.33.

MS (EI+, [M]+) 119.0.

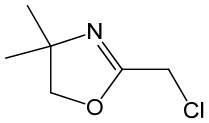


2-(azidomethyl)-4,5-dihydrooxazole (6)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94-3.89 (m, 4H), 4.37-4.32 (t, 2H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 163.18, 68.24, 54.47, 46.62.

MS (EI+, [M]+) 126.0.



2-(chloromethyl)-4,4-dimethyl-4,5-dihydrooxazole (8)

Color and State: Colorless Oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28(s, 6H), 4.02 (s, 2H), 4.06 (s, 2H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 160.90, 80.00, 67.64, 36.54, 28.02.

APPENDIX B

EXPLORING THE SYNTHESIS OF MOLECULES WITH THE HYDRAZINE MOEITY VIA A THERMOLYTIC REARRANGEMENT REACTION

B.1 Hydrazine Background

Hydrazines are important compounds and have previously been introduced in Chapter 1 section 1.1.1. To summarize, the hydrazine moeity can be found in several molecule classes that are applicable in the chemical industry, such as in pesticides, [119] propellants, [120] and pharmaceuticals. [121] Current hydrazine synthesis procedures usually involve an excess of hazardous strong acids and bases[122] which may produce a large amount of aqueous salt waste. A rare method of hydrazine formation is through an analogous Curtius (Aza-Curtius) photolysis reaction (Fig. B.1). The Aza-Curtius reaction begins with phenylcarbamoyl azide (1) and is exposed to a 254 nm light source in methanol to form methyl 2-phenylhydrazinecarboxylate (2) in 65% yield. [31]

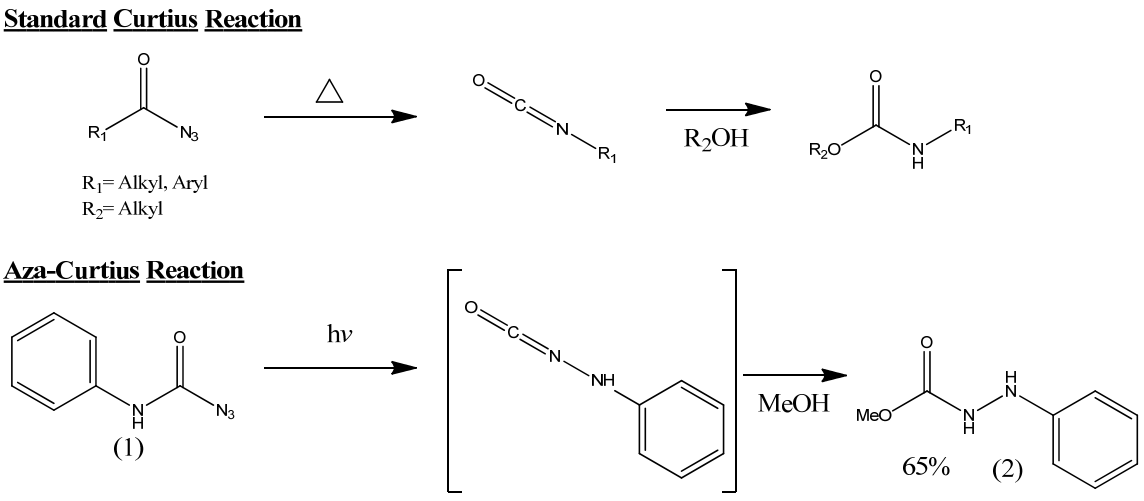
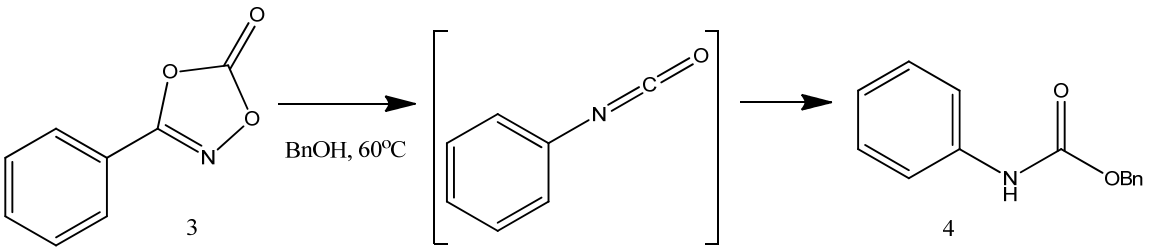


Figure B.1: The standard Curtius reaction[123, 124] and the Aza-Curtius reaction.

Even though this reaction avoided the use of excess acids and bases, this reaction suffers from many limitations and has not been optimized or studied since their initial publications. The Aza-Curtius reaction only has moderate yields and photolysis is not viable in an industrial setting. It may be possible to perform this type of reaction through a thermolysis method.

B.2 Heterocycle Rearrangements

A heterocyclic thermolysis could be a potential route to a hydrazine. One paper demonstrated a thermal rearrangement of 3-phenyl-1,4,2-dioxazol-5-one (3) in benzyl alcohol to benzyl phenylcarbamate (4) (Fig. B.2). [125]



3 4

Figure B.2: Dioxazolone rearrangement to a carbamate product

The Aza-analog to this reaction has never been preformed, but could be a possible method to a protected, mono-substituted hydrazine (6) (Figure B.3).

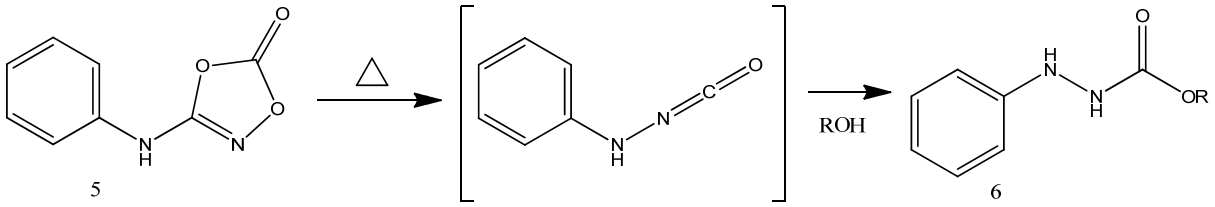


Figure B.3: Proposed Dioxazolone rearrangement to a protected, mono-substituted hydrazine product

For this proposed reaction to be carried out, 3-(phenylamino)-1,4,2-dioxazol-5-one (5) would have to be synthesized. There is no instance in literature where (5) has been synthesized. Another method that has been shown in literature to form a N-N bond is through the photolysis of 1,4-dimethyl-1*H*-tetrazol-5(4*H*)-one (7) to 1,2-dimethyldiaziridin-3-one (8) in an inert gas matrix (12 K) (Fig. B.4). [126] Other aziridinones, such as 1,2-di-*tert*-butyldiaziridin-3-one, have been reported to produce methyl 1,2-di-*tert*-butylhydrazinecarboxylate (10) in acidic methanol conditions (Fig. B.4). [127]

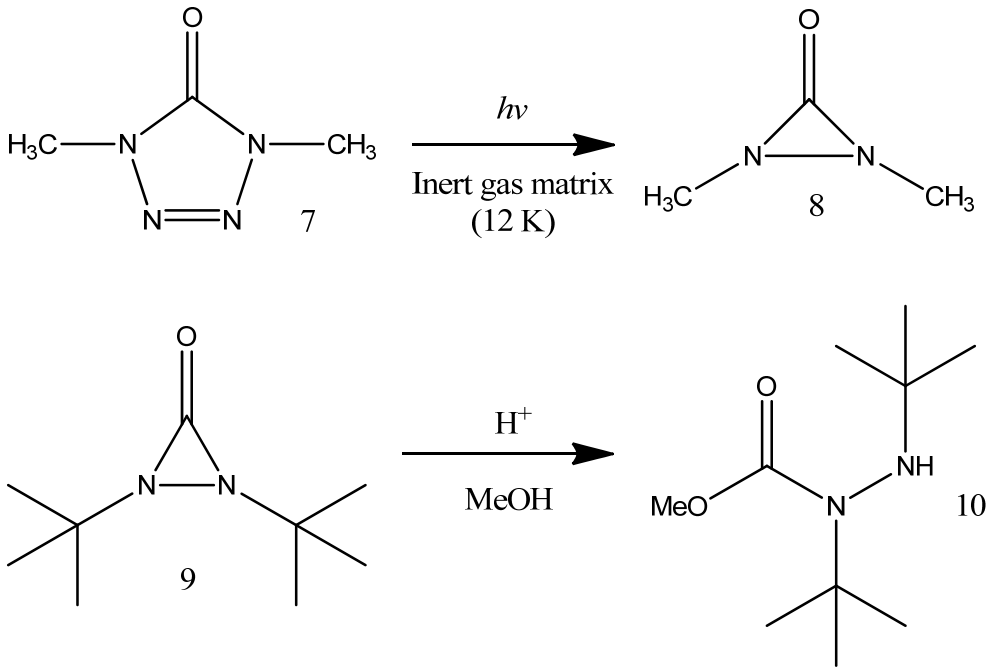


Figure B.4: Tetrazolines and aziridinone compounds to hydrazine containing products

These methods are novel in their synthetic procedures, but aziridinones are difficult to produce at ambient conditions (12 K) and use photolytic techniques, which is not suitable for large scale syntheses. For our interest, a monosubstituted tetrazoline would be of interest in using heat to initiate a rearrangement. A proposed reaction is outlined in Figure B.5.

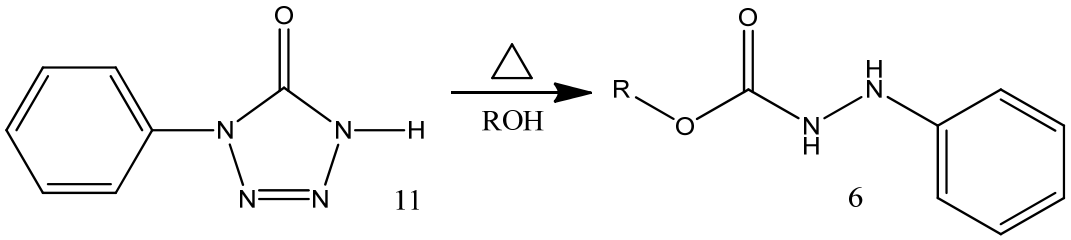


Figure B.5: Tetrazolines and aziridinone compounds to hydrazine containing products

To select a temperature and appropriate solvent for the thermolytic decomposition study, compound 1 was studied using differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) (Fig. B.6).

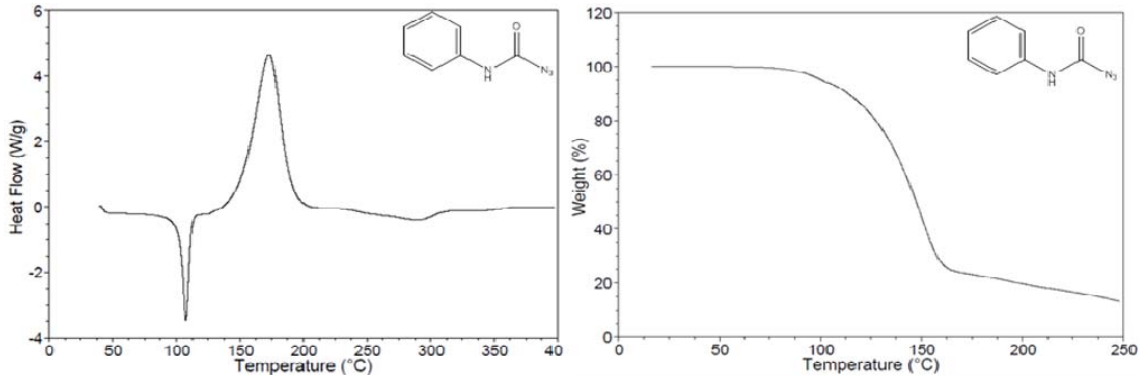


Figure B.6: The DSC and TGA analysis of phenylcarbamoyl azide

The DSC showed one thermal event at 107°C (phenylcarbamoyl azide melting point) and a second, broad thermal event begins at about 130°C. According the TGA analysis the temperature at which there is a significant rate of mass loss is about 125°C. This thermal event in both the DSC and TGA seems to coincide with a decomposition of the carbamoyl azide. Using 125°C as approximate starting point, we decided to use cyclohexanol (boiling point: 160°C) as the solvent for this thermolysis study. To test carbonyldiimidazole-mediated Aza-Lossen rearrangement, 3-(phenylamino)-1,4,2-dioxazol-5-one (5) was synthesized in two steps (Fig. B.7).

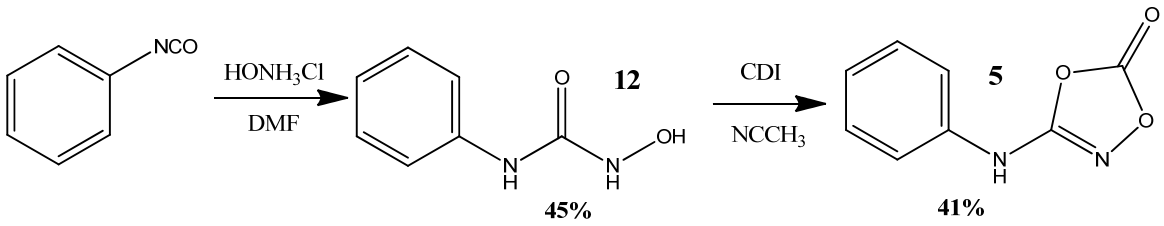


Figure B.7: Synthesis of 3-(phenylamino)-1,4,2-dioxazol-5-one (4)

In the first step, phenylisocyanate is reacted with hydroxylamine to form 1-hydroxy-3-phenylurea (12) in 45% yield. Compound 12 was then reacted with carbonyldiimidazole (CDI) to form the new dioxazolinone (5) in 41% yield. To the best of our knowledge, this the first time 5 has been synthesized. To test a tetrazolinone rearrangement, 1-phenyl-1*H*-tetrazol-5(4*H*)-one (11) was synthesized in one step, following a procedure in literature (Fig. B.8). [128]

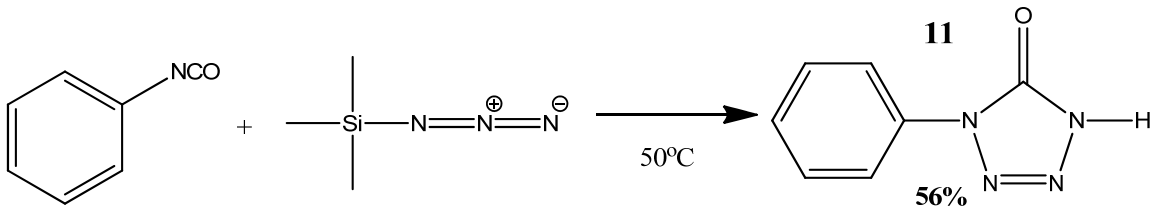


Figure B.8: Synthesis of 1-phenyl-1*H*-tetrazol-5(4*H*)-one (11)

Phenylisocyanate was reacted with trimethylsilyl azide without solvent. Compound 11 was isolated in 56% yield. Each of the compounds of study (1, 5, and 11) was heated to 135°C for about 13 hours at a concentration of 1 mmol of reagent per 50 mL of cyclohexanol. Surprisingly, instead of the synthesis of the expected hydrazine rearrangement product, all of the compounds underwent a condensation reaction with cyclohexanol to form cyclohexyl carbamate (13) (Fig. B.9).

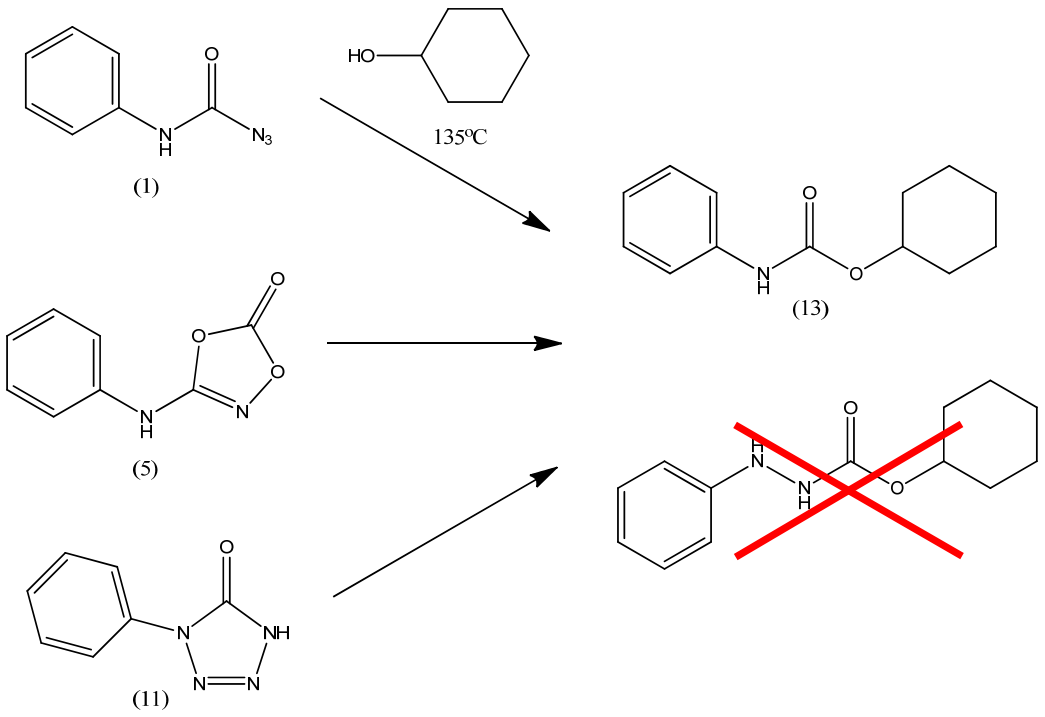


Figure B.9: Condensation with cyclohexanol to cyclohexyl phenyl carbamate

B.4 Conclusions

Three compounds (1,5,11) were synthesized to attempt a thermolytic rearrangement to hydrazine products. The reactions took place in cyclohexanol at 135°C, but at the given conditions, the condensation reaction to 13 was more favorable. While the photolysis reaction seems to be successful in producing hydrazine products, thermal decomposition is not a suitable route.

B.4 Experimental

Synthesis of phenylcarbamoyl azide (1)

In a 50 mL flask, 20 mL acetonitrile was added. After sparging with nitrogen, 0.5 mL of benzaldehyde (0.48 g, 0.0045 mol), stirred for 1 minutes, and 2.56 g (1.5 eqv, 0.0068 mol) of Iodobenzene diactate solid was added portionwise (mixture is heterogeneous). 1.5 mL (0.0112 mol, 2.5 eqv) of trimethylsilyl azide is added dropwise to solution (mixture is homogeneous). After the the mixture was stirred for 4 hr at room temperature the solvent was evaporated. Three recrystallizations were done by dissolving crude in ethyl acetate and using hexane as anti-solvent. After filtering, 0.35 g of (1) was recovered (49% yield).

Synthesis of 1-hydroxy-3-phenylurea (12)

In a 250 mL flask, 100 mL of dimethylformamide (DMF) was added under nitrogen. Portionwise, 10 g (0.143 mol) hydroxylamine hydrochloride salt is added and the flask is cooled in an ice bath. To the solution, 10 g of triethylamine was added to make a heterogeneous solution. The salt is filter and washed with DMF. The liquid filtrate was placed back under nitrogen and 17.14 g (0.143 mol) of Phenylisocyanate is then added dropwise. The DMF solvent was evaporated under heat and vacuum. The product was isolated from the crude by dissolving in ethyl acetate and precipitating from hexane. 9.58 g (44% yield) of (12) was isolated.

Synthesis of 3-(phenylamino)-1,4,2-dioxazol-5-one (5)

In a 25 mL flask equipped with a stir bar, 0.3 g (0.002 mol) of phenylhydroxyurea was added and purged with nitrogen. The solvent (5 mL of acetonitrile) was added and the solution (heterogeneous) was stirred. 0.32 g (0.002 mol) of carbonyldiimidazole (CDI)

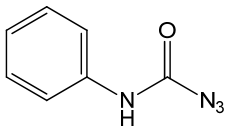
was added portionwise to the mixture (reaction becomes homogeneous). The mixture was stirred for 3 hrs and dichloromethylene was added to precipitate solid products. The solid was filtered and dissolved in water. The aqueous solution was mixed with with 1M HCl and organics were extracted with ethyl acetate. The ethyl acetate layer was dried with $MgSO_4$, filtered, and the solvent removed vacuum. 146 mg (41%) of (5) was isolated.

Synthesis of 1-phenyl-1*H*-tetrazol-5(4*H*)-one (11)

In a 25 mL round bottom flask equipped with a stir bar and condenser, 2.20 g (0.0185 mol) of phenyl isocyanate was added. Then 3.15g (0.027 mol) of trimethyl silyl azide was added while stirring. The neat mixture was heated to 50°C and stirred. After 24 hours, excess trimethylsilyl azide was removed by vacuum to obtain a crude oil. The mother liquor was triturated with toluene to get 1.7 g (56%) of (11).

Representative Synthesis of cyclohexyl phenylcarbamate (13)

In a 200 mL round bottom flask equipped with a stir bar and condenser, 0.163 g (0.001 mol) of starting material (1,4, and 5) was added. The reaction vessel was purged with nitrogen and 50 mL of cyclohexanol was added while stirring. The reaction was heated to 135°C and stirred for 13 hrs. The solvent was removed under vacuum. The crude product was passed through an alumina column (pH = 7.2) using ethyl acetate as eluent.



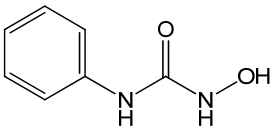
Phenylcarbamoyl azide (1)

Color and State: White solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (broad s, 1H), 7.15-7.11 (t, 1H), 7.34-7.30 (t, 2H), 7.45-7.43 (d, 2H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 154.13, 136.69, 129.30, 124.77, 119.38.

M.P. 103°C (Lit. Reports 108°C [61])

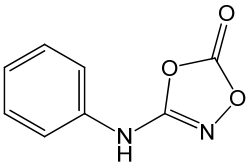


1-hydroxy-3-phenylurea (12)

Color and State: White solid

^{1}H NMR (400 MHz, DMSO) δ 6.94-.6.98 (t, 1H), 7.22-7.24 (t, 2H), 7.60-7.62 (d, 2H), 8.73 (s, 1H), 8.81 (s, 1H), 8.94 (s, 1H).

^{13}C NMR (400 MHz, DMSO) δ 159.02, 139.47, 128.73, 122.54, 119.55



3-(phenylamino)-1,4,2-dioxazol-5-one (5)

Color and State: White solid

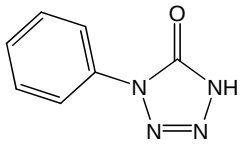
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.43 (m, 5H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 156.02, 152.49, 130.56, 129.05, 128.73, 126.11.

MS (ES-, [M]-) Found: 176.6, MW: 178.1.

E.A. Theory: C: 53.94, H: 3.39, N: 15.73 Found: C: 54.01, H: 3.48, N: 15.75

M.P. 135°C.

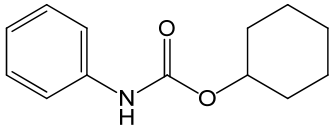


1-phenyl-1*H*-tetrazol-5(4*H*)-one (11)

Color and State: White solid

^{1}H NMR (400 MHz, DMSO) δ 7.41-7.43 (t, 1H), 7.54-7.56 (t, 2H), 7.84-7.86 (d, 2H).

^{13}C NMR (400 MHz, DMSO) δ 150.26, 134.21, 129.47, 127.58, 119.52



Cyclohexyl phenylcarbamate (13)

Color and State: White solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98-1.26(m, 9H), 4.76 (m, 1H), 6.70 (broad s, 1H), 7.03-7.05 (t, 1H), 7.28-7.30 (t, 2H), 7.38-7.39 (d, 2H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 153.33, 138.25, 129.12, 123.27, 118.67, 73.71, 32.03, 25.48, 23.88.

HR-MS Exact Mass Calculated: 219.130, Exact Mass Found: 219.1262

APPENDIX C

THE SYNTHESIS OF ESTER PROTECTED AMINATING AGENTS FOR THE SYNTHESIS OF PROTECTED HYDRAZINES

C.1 Poly-Substituted Hydrazines Background

Poly-substituted hydrazine derivatives are important to a variety of applications in organic chemistry and industry. [16, 129] An outline of mono-substituted hydrazine synthesis was reported Chapter 1, section 1.1.2. However, tri-substituted and tetra-substituted hydrazines are more challenging in synthesis. Fig. C.1 demonstrates some example syntheses of trimethylhydrazines.

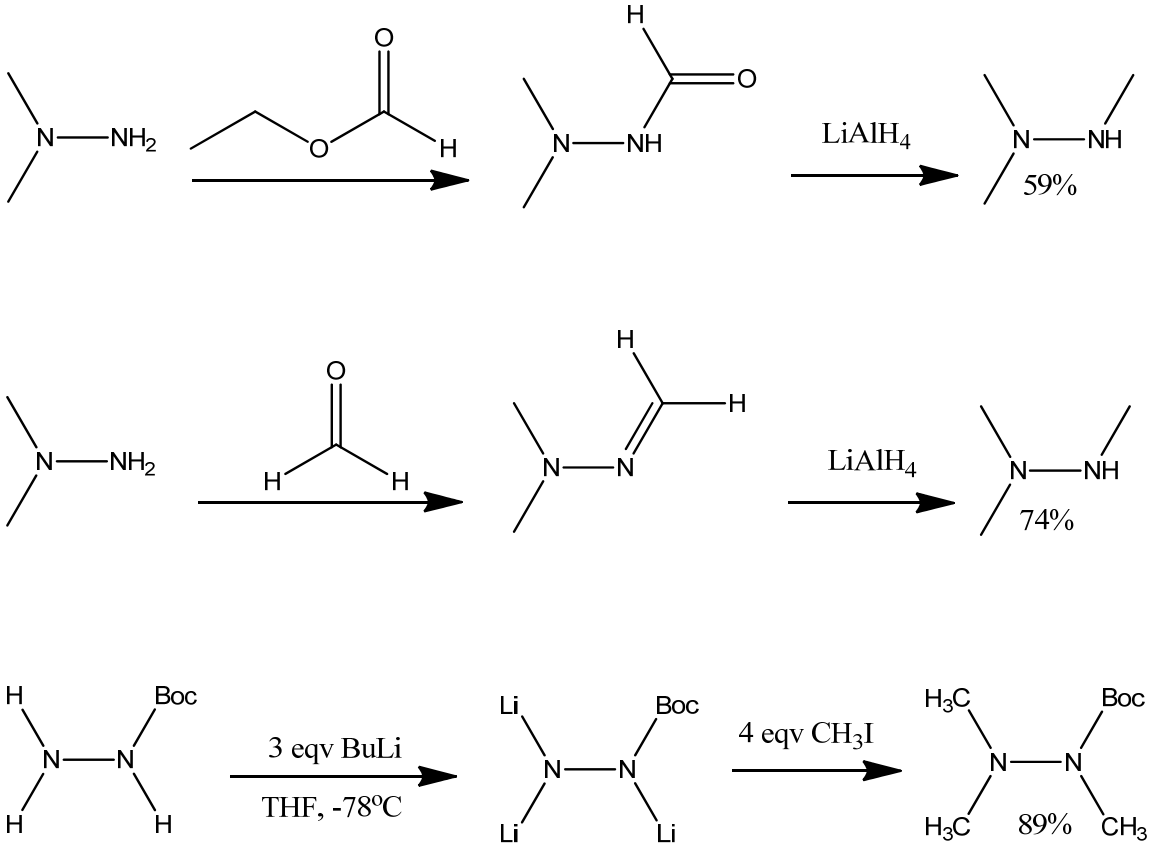


Figure C.1: Synthesis of trimethyl hydrazine and Boc-protected trimethyl hydrazine

Direct amination of amines are an alternative to the use of oxidation/reduction reaction that utilize strong acids and bases. [130] One of the most powerful classes of aminating agents for the synthesis of the N-N bonds are ortho-mesitylenesulfonylhydroxylamines. [131] In 2011, Baburaj et. al. showed that *N*-Boc-*O*-tosyl hydroxylamine was an efficient agent for electrophilic amination for synthesizing β-NBoc protected aryl and alkyl hydrazines. [132] However, the study only demonstrated the synthesis of mono-substituted hydrazines. This study explores the synthesis of poly-substituted hydrazines with direct amination.

C.2 Synthesis of Aminating Agents

The reaction of *N*-Boc-*O*-mesityl hydroxylamine (synthesized in lab) was shown to also be an effective agent in N-N coupling. The reaction with *p*-anisidine formed a hydrazine carboxylate in 99% (Fig. C.2).

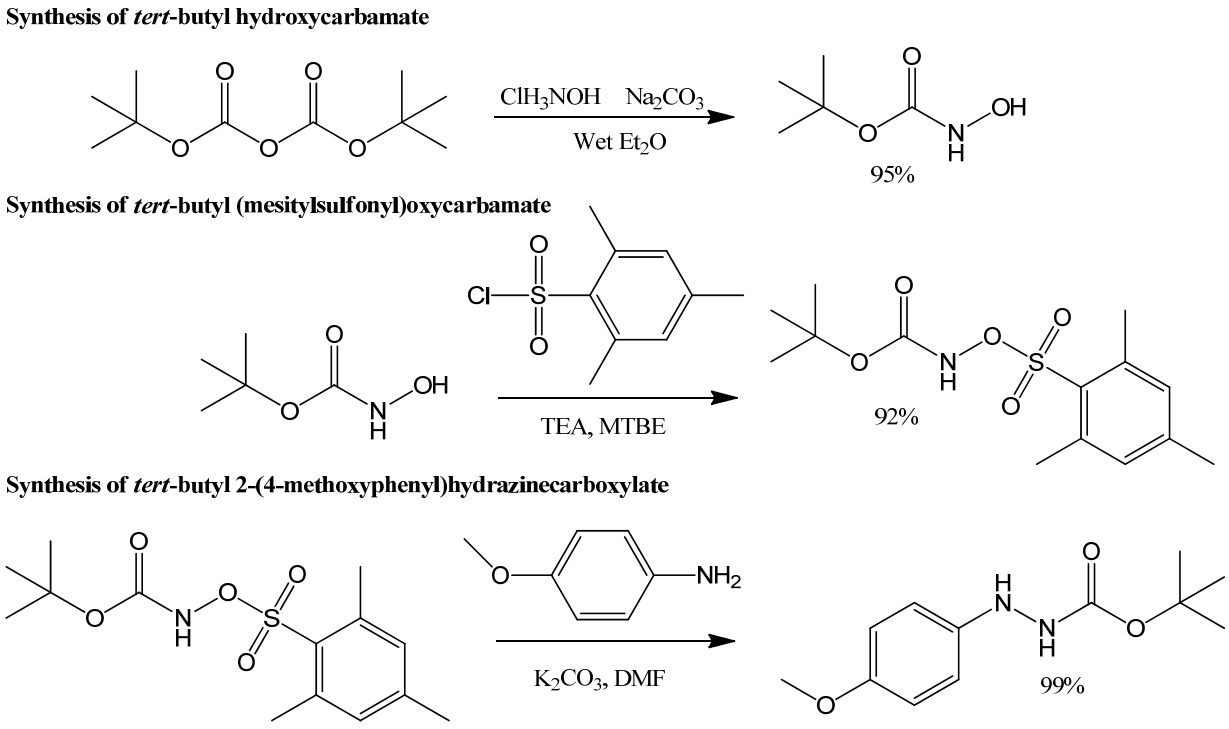


Figure C.2: Total Synthesis of *tert*-butyl-2-(4-methoxyphenyl)hydrazine carboxylate by electrophilic amination

At the labs at AmPac (industrial sponsor), a parallel study with a less nucleophilic aryl amine was performed. The reaction time for the amination was several hours longer than the reaction in Fig. C.2 (2.5 hrs). While the yield was moderate (approx. 50%), the reaction did not progress as well as previous examples. Subsequent studies by AmPac revealed that after about 12 hours the *N*-Boc-*O*-mesityl hydroxylamine had decomposed. In an effort to obtain a higher yield, we explored the synthesis of new, alternative N-protected-*O*-mesitylhydroxylamines that could potentially be more stable in the reaction conditions. The first compound studied was methyl (mesitylsulfonyl)oxycarbamate (Fig C.3).

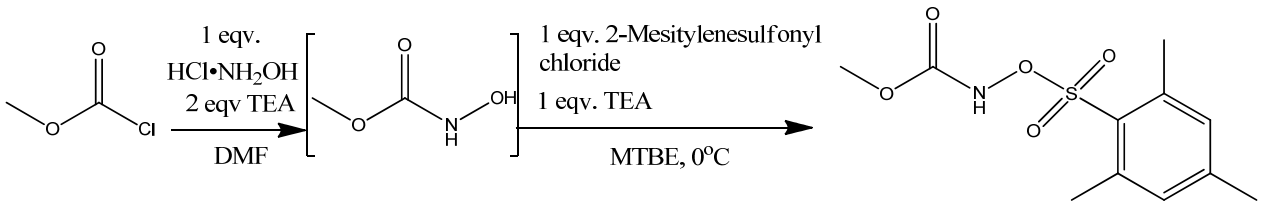
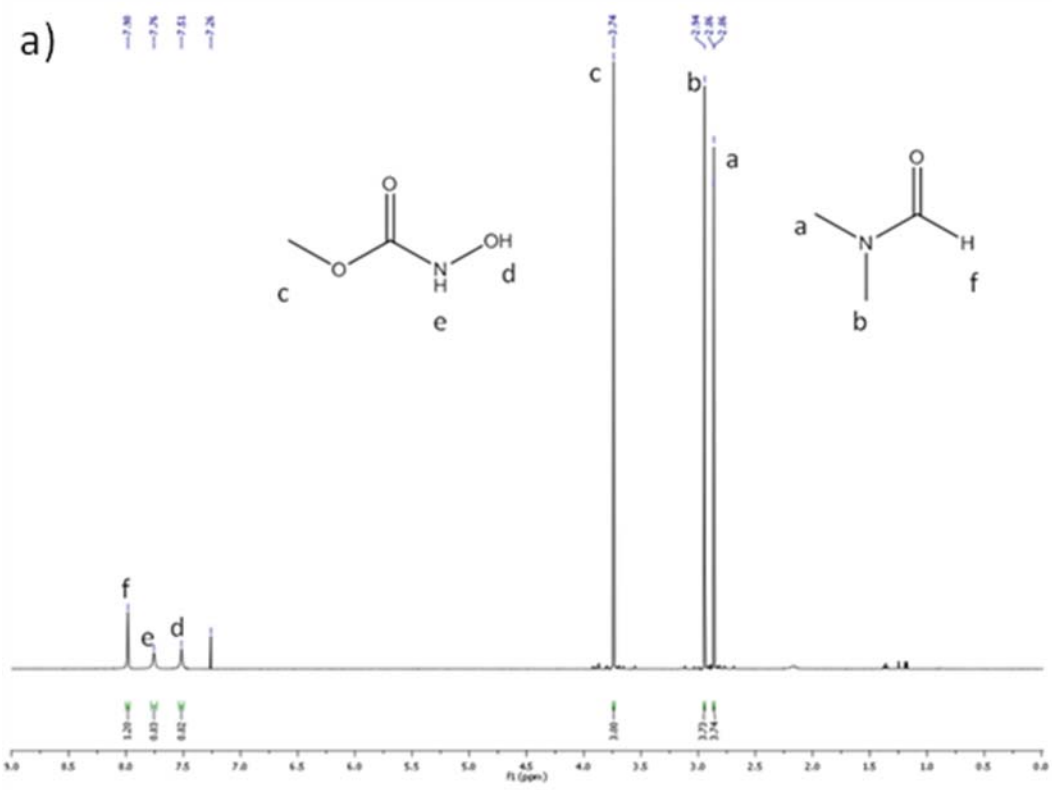


Figure C.3: Synthesis of methyl (mesitylsulfonyl)oxycarbamate for amination study

The reaction had to be done in one pot without, because the intermediate compound, methyl hydroxycarbamate, could not be isolated at room temperatures. ^{1}H NMR shows the presence of the hydroxycabamte when DMF is present (Fig. C.4a), but when DMF was removed in a vacuum oven at 60°C for 2 hours, the 1H NMR shows decomposition of the product (Fig. C.4b).



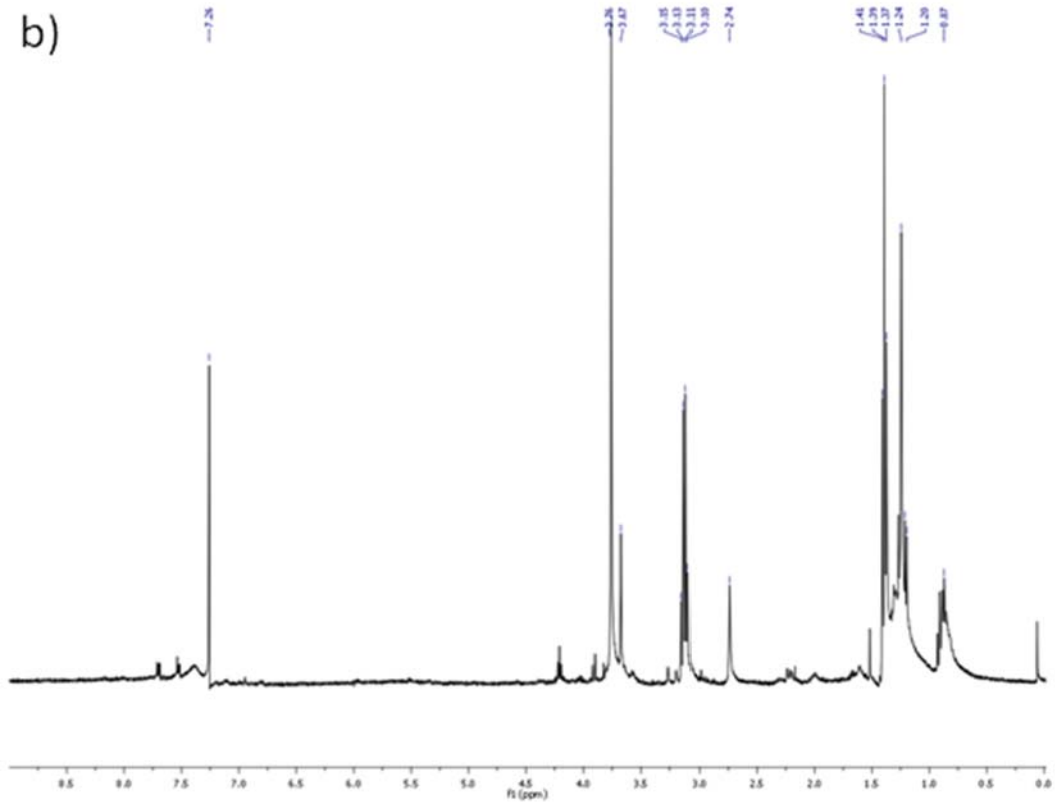


Figure C.4: a) ^{1}H spectra of methyl hydroxycarbamate with DMF b) ^{1}H spectra of decomposed product after 2 hrs. in a vacuum oven at 60°C

The final product, methyl (mesitylsulfonyl)oxycarbamate was obtained at about 50% yield (90% purity) in one reaction, but subsequent, repeat reactions did not yield appreciable amounts of the product. The reaction to the product was deemed irreproducible, so we looked to find a more stable alternative. Isobutyl hydroxycarbamate has been shown in literature as an isolable species, [133] so we tried to synthesize the isobutyl (mesitylsulfonyl)oxycarbamate (Fig. C.5).

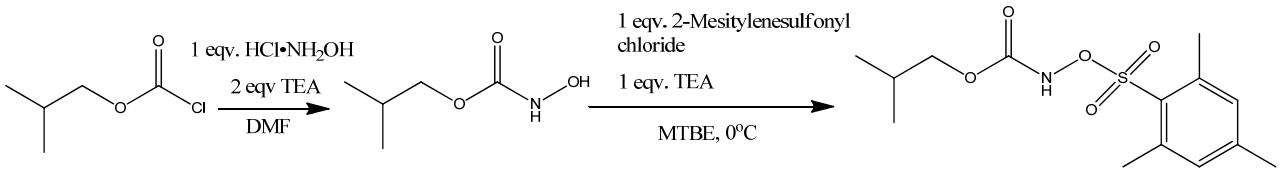
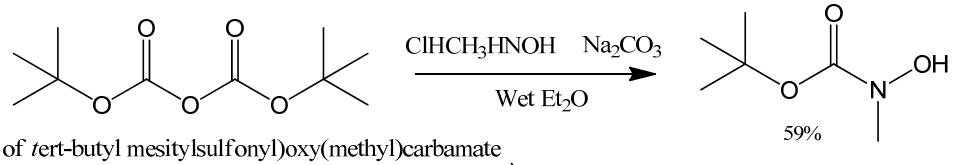


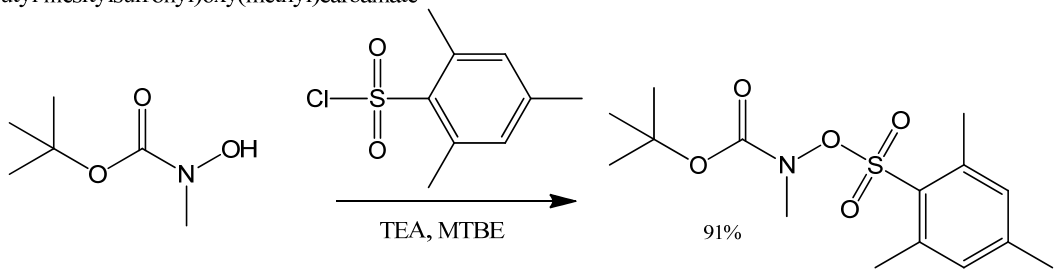
Figure C.5: Synthesis of isobutyl (mesitylsulfonyl)oxycarbamate for amination study

In this case, the isobutyl hydroxycarbamate was isolated as a pure oil in 63% yeild, but formation of the product in the second step was unsuccessful after several attempts. It was apparent that *tert*-butyl (mesitylsulfonyl)oxycarbamate was the most suitbable compound for electrophilic amination reactions. It was also of interest to see if the electrophilic amination reactions could take place with an N-substituted *tert*-butyl (mesitylsulfonyl)oxycarbamate (Fig. C.6).

Synthesis of *t*ert-butyl hydroxy(methyl)carbamate



Synthesis of *t*ert-butyl mesitylsulfonyl)oxy(methyl)carbamate



Synthesis of *t*ert-butyl 2-(4-methoxyphenyl)-1-methylhydrazinecarboxylate

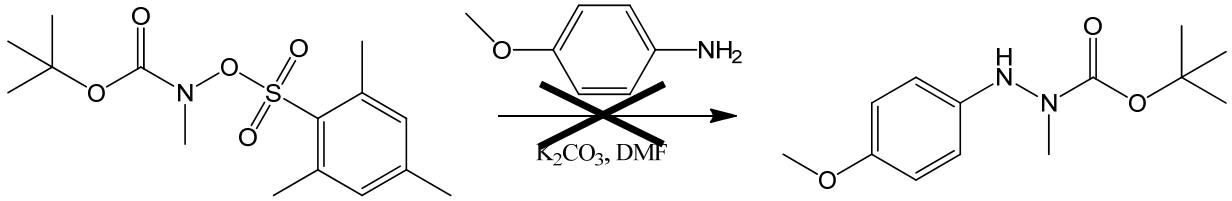


Figure C.6: Total Synthesis of tert-butyl-2-(4-methoxyphenyl)-1-methylhydrazinecarboxylate by electrophilic amination.

Using a methylated hydroxylamine hydrochloride salt, we successfully synthesized the *tert*-butyl hydroxyl(methyl)carbamate (59%) and the *tert*-butyl mesitylsulfonyl)oxy(methyl) carbamate (91%). Unfortunately, the electrophilic amination of *p*-anisidine with these new methylated aminating agents was unsuccessful in producing a Boc-protected disubstituted hydrazine. There could be two main factors in the ineffectiveness of *N*-substituted amination: steric hinderance of the methyl group or electronic effects. The methyl group could provide enough bulk to sterically hinder access of the amine to the aminating agent during a S_N2 reaction. Also, since the electrophilic amination depends on electrophilic nature of the nitrogen in the tert-butyl mesitylsulfonyl)oxy(methyl) carbamate, an added electron donating methyl group on the nitrogen could make the nitrogen a much less reactive center. We did not pursue this reaction any further.

C.3 Conclusions

An effort was made to produce substituted aminating agents for the purpose of synthesizing ester protect di- and trisubstituted hydrazines. Tert-butyl (mesitylsulfonyl)oxycarbamate was found to suitable the synthesis of protected mono-substituted hydrazines, but methyl (mesitylsulfonyl)oxycarbamate and isobutyl (mesitylsulfonyl)oxycarbamate (not synthesized in literature) could not be isolated. Tert-

butyl mesitylsulfonyl)oxy(methyl) carbamate, a methylated aminating group, was successfully synthesized for the first time, but it was not a successful reagent for the formation of a di-substituted hydrazine.

C.4 Experimental

Synthesis of *tert*-butyl hydroxycarbamate

In a 250 mL round bottom flask with a stir bar, 6 g (0.0875 mol) hydroxylamine hydrochloride and 38 mL diethyl ether solvent was added. The heterogenous solution was stirred vigorously and 6 g (0.0575 mol) of sodium carbonate was added to the flask. Dropwise, 5 mL of water was added into the reaction mixture. The suspension was stirred for 1 hr, and then cooled in an ice water bath. To the cool reaction mixture, a solution of 12.55 g (0.0575 mol) di-tert-butyl dicarbonate in 12.5 mL diethyl ether was added over 30 min (Adding too fast will generate uncontrollable gas accumulation). The reaction mixture was heated to room temperature and stirred for 3 hours. The reaction was then filtered to remove the solid and washed diethyl ether. The filtrate was put under vacuum to evaporate the solvent to mother liquor. Upon addition of cyclohexane the product was crystallized as colorless needles (2 crops). 7.3 g (95%) of product was isolated.

Synthesis of *tert*-butyl (mesitylsulfonyl)oxycarbamate

In a 100 mL flask, 3.25 g (0.0147 mol) of 2-Mesitylenesulfonyl chloride and 2 g (0.0147 mol) of *tert*-butyl hydroxycarbamate was added dissolved with 34 mL of methyl *tert*-

butyl ether (MTBE). The flask was purged with Argon and cooled to 0°C in a ice water bath. To the cool solution, 2.1 mL (0.015 mol) of Triethylamine was added dropwise over 1.5 hr. The reaction was then stirred for an additional 2 hr. The solution was filtered to remove salt. The solvent was then evaporated using rotary evaporation until a small amount of solvent is left (Did not let product crystallize). Hexane was added to the mother liquor to crystallize product (white solid). 4.27 g (92%) of product was recovered.

Synthesis of *tert*-butyl 2-(4-methoxyphenyl)hydrazinecarboxylate

In a 50 mL round bottom flask equipped with a stir bar, 0.5 g (0.0041 mol) of p-anisidine and 0.73 g (0.0052 mol) of K_2CO_3 was added. The reaction vessel was purged with nitrogen. 5 mL of DMF was added while stirring and cooled to 0°C in an ice bath. To the cold solution, 0.154 g of Boc-MSH is added portionwise. The reaction was heated to room temp (about 22°C) and stirred for 2.5 hrs. Water was added to precipitate the solid product and filtered. Ethyl acetate dissolved the solid and $MgSO_4$ was used to dry the solution. Some solvent was removed under vacuum and hexane was added to crystallize product. 0.963 g was isolated (99% yield).

Synthesis of methyl hydroxycarbamate (in DMF)

In a 50 mL round bottom flask equipped with a stir bar, 0.45 g $NH_2OH.HCl$ (0.00647 mol) and 20 mL of DMF was added. The vessel was sparged with nitrogen. 0.5 mL (0.00647 mol) chloromethylformate was added. The reaction mixture was cooled in an ice bath and 1.8 mL (0.01294 mol) of triethylamine was added slowly. The reaction mixture was allowed to reach room temp and stirred overnight. The solid salt was filtered

and the liquid mixture had the most (but not all) of solvent removed under vacuum at 60°C.

Synthesis of methyl (mesitylsulfonyl)oxycarbamate

In a 50 mL round bottom flask equipped with a stir bar, 0.45 g $NH_2OH.HCl$ (0.00647 mol) and 20 mL of DMF was added. The vessel was sparged with nitrogen. 0.5 mL (0.00647 mol) chloromethylformate was added. The reaction mixture was cooled in an ice bath and 1.8 mL (0.01294 mol) of triethylamine was added slowly. The cold reaction stirred for 30 minutes. 1.41 g (0.00657 mol) of solid 2-mesitylenesulfonyl chloride was added to the flask. 0.9 mL (0.00647 mol) of triethylamine was then added to the cold flask. The reaction mixture was allowed to reach room temp and stirred overnight. Water was added to precipitate a white solid and dissolve salt. The solid was filtered from the liquid. The wet solid was dissolved in DCM and water was added in a separatory funnel. The organic layer was removed, dried with $MgSO_4$, and the solvent was evaporated under vacuum and heat. The crude was purified on a neutral alumina column with ethyl acetate/hexane (20:80 and 80:20). 1.2 g (68%) of product recovered in about 90% purity.

Synthesis of isobutyl hydroxycarbamate

In a 50 mL round bottom flask equipped with a stir bar, 1 g $NH_2OH.HCl$ (0.0144 mol) and 20 mL of DMF was added. The vessel was sparged with nitrogen. 1.97 g (0.0144 mol) isobutychlorolformate was added. The reaction mixture was cooled in an ice bath and 4 mL (0.01294 mol) of triethylamine was added slowly. The reaction mixture was

allowed to reach room temp and stirred overnight. The salt was filtered and water and ethyl acetate were added. The mixture was added to a separatory funnel and washed with water 3 times. The organic layer was separated, dried with $MgSO_4$, and the solvent was evaporated under vacuum. The crude was purified on a silica column with ethyl acetate/hexane (20:80). 1.21 g (63%) of product isolated.

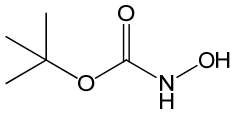
Synthesis of *tert*-butyl(methyl) hydroxycarbamate

In a 100 mL round bottom flask with a stir bar, 2.44 g (0.029 mol) N-methylhydroxylamine hydrochloride and 14 mL diethyl ether solvent was added. The heterogenous solution was stirred vigorously and 2 g of sodium carbonate was added to the flask. Dropwise, 0.4 mL of water was added into the reaction mixture. The suspension was stirred for 1 hr, and then cooled in an ice water bath. To the cool reaction mixture, a solution of 4.18 g (0.0435 mol) di-*tert*-butyl dicarbonate in 10 mL diethyl ether was added over 30 min (Adding too fast will generate uncontrollable gas accumulation). The reaction mixture was heated to room temperature and stirred for 3 hours. The reaction was then filtered to remove the solid and washed diethyl ether. The filtrate was put under vacuum to evaporate solvent. 2.54 g (59%) of product was isolated as an oil.

Synthesis of *tert*-butyl (mesitylsulfonyl)oxy(methyl)carbamate

In a 250 mL flask, 3.75 g (0.0171 mol) of 2-mesitylenesulfonyl chloride and 2.52 g (0.0171 mol) of *tert*-butyl(methyl) hydroxycarbamate was added dissolved with 40 mL of methyl *tert*-butyl ether (MTBE). The flask was purged with argon and cooled to 0°C in a

ice water bath. To the cool solution, 1.73 mL (0.0171 mol) of triethylamine was added dropwise over 1.5 hr. The reaction was then stirred for an additional 2 hr. The solution was filtered to remove salt. The solvent was then evaporated using rotary evaporation until a small amount of solvent is left (Did not let product crystallize). Hexane was added to the mother liquor to crystallize product (white solid). 5.2 g (91%) of product was recovered.



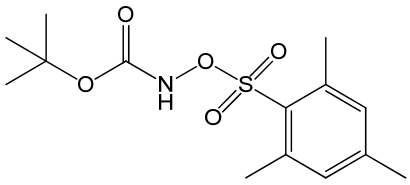
***tert*-butyl hydroxycarbamate**

Color and State: White needles

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 158.80, 82.18, 28.16.

MP 52-54 °C



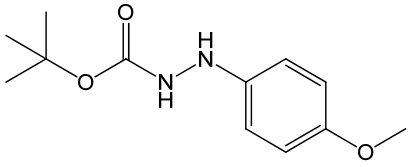
***tert*-butyl (mesitylsulfonyl)oxycarbamate**

Color and State: White solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 9H), 2.32 (s, 3H), 2.67 (s, 6H), 6.99 (s, 2H), 7.60 (s, 1H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 154.12, 144.39, 141.92, 131.62, 128.46, 83.80, 27.71, 23.11, 21.11.

MP 98-100 °C

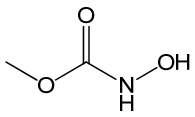


***tert*-butyl 2-(4-methoxyphenyl)hydrazinecarboxylate**

Color and State: White solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31(s, 9H), 3.79 (s, 3H), 6.85-6.87 (d, 2H), 7.34-7.36 (d, 2H).

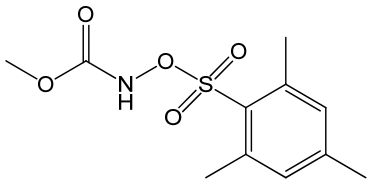
^{13}C NMR (400 MHz, $CDCl_3$) δ 158.48, 156.41, 130.45, 121.89, 114.36, 81.47, 55.65, 26.55



methyl hydroxycarbamate (in DMF)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74(s, 3H), 7.51 (broad s, 1H), 7.76 (broad s, 2H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 162.83, 52.86.



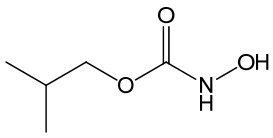
methyl (mesitylsulfonyl)oxycarbamate

Color and State: White solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32(s, 3H), 2.67 (s, 6H), 3.63 (s, 3H), 6.99 (s, 2H), 7.88 (s, 1H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 156.01, 144.63, 141.93, 131.68, 128.16, 53.69, 22.87, 21.16.

MS (EI+, [M]+) 273.0.

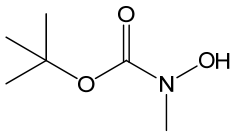


isobutyl hydroxycarbamate

Color and State: Colorless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, 6H), 1.92 (septuplet, 1H), 3.93 (d, 2H), 7.40 (s (br) 1H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 159.77, 72.29, 27.90, 18.88

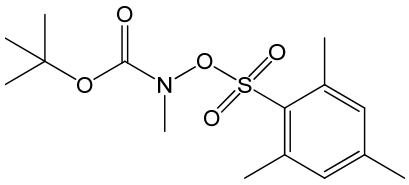


***tert*-butyl hydroxy(methyl)carbamate**

Color and State: Colorless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9H), 3.15 (s, 3H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 157.76, 82.01, 37.92, 28.43.



tert-butyl (mesitylsulfonyl)oxy(methyl)carbamate

Color and State: White solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 9H), 2.32 (s, 3H), 2.65 (s, 6H), 3.24 (s, 3H), 6.98 (s, 2H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 156.38, 144.31, 142.05, 131.78, 128.46, 83.53, 40.38, 27.76, 23.55, 21.23.

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